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SECTION ONE

Pain Management

CHAPTER ONE

Overview of Pain Management

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe how a pain signal travels through the nervous system to the brain.
- Differentiate acute, chronic benign, and cancer pain.
- Discuss the goals of pain treatment for each type of pain.
- State the types of clinicians who practice pain management.
- Understand the concept of interdisciplinary pain management.
- Understand current practice patterns for chronic benign pain and cancer pain.
- Describe the objectives of palliative care and hospice programs.
- Identify patients who are eligible for hospice care.
- Describe the common reasons for undertreatment of pain with opioids.
- Define substance abuse, addiction, and pseudoaddiction.
- Describe opioid phobia.

Terminology

Acute pain:	Short-term pain experienced after surgery or a traumatic injury.
Chronic benign pain:	Pain from problems that are neither fatal nor curable.
Central pain:	Pain that results from injury or disease in the spinal cord or brain.
Dependence:	A withdrawal syndrome develops if a medication is stopped suddenly.
Descending pathways:	Nerve fibers that travel down the spinal cord from the brain and inhibit pain signals.
Diversion:	Utilization of selling or abusing medication prescribed for a medical condition.
Fellowship trained:	Having 1 year or more of additional medical training specifically in pain management in an accredited pain management program.
Neuralgic pain:	Localized pain resulting from damage to a single nerve.
Neuron:	A nerve cell, including its body and its dendrites (very short branch-like extensions of the cell body) and axon.
Neuropathic pain:	Pain resulting from damage to the nerves.
Nerve:	A bundle of nerve axons (outside the brain or spinal cord) that run together within a connective tissue sheath.
Nerve fiber:	A long, typically singular branch of the nerve cell that relays messages to and from the area it serves. These branches can be several feet long in the extremities. A fiber is also called an axon.
Nerve tract:	A bundle of nerve axons that run together within the spinal cord or brain, functioning in a manner similar to a nerve.
Nociception:	The sensation of pain.
Opioid phobia:	An irrational fear of using strong opioid analgesics.
Peripheral neuropathy:	Pain in areas such as the feet and/or hands resulting from damage to the long nerve fibers that supply the limbs.
PRN:	An acronym made from the Latin 'pro re nata', which means as needed. It is typically used in medical orders and prescriptions.
Pseudoaddiction:	Behaviors (that mimic addictive behaviors) exhibited by patients with inadequately treated pain.
Sensory nerve:	This is a nerve that carries sensation signals, including pain.
Somatic pain:	Sharp, localized pain originating from the skin, muscles, tendons, ligaments, and bones.
Synapse:	This is a communication point between nerves. The synapse consists of a gap between the cells; chemical messengers cross the gap to relay a signal from one nerve to the next. Tolerance: The need for increased doses of medication over time to achieve the same level of pain control.
Visceral pain:	Poorly localized pain originating from internal organs.
Visual analog:	A pain severity rating scale.

Introduction

The first goal of medicine is to cure disease. In many cases, however, the disease cannot be cured. In these cases, the goal becomes management of the symptoms of the disease so that the patient can live a normal life. For patients suffering from a variety of different diseases, pain is the symptom that causes the most severe disruption of day-to-day activities. Between 10% and 15% of the population suffers from chronic pain severe enough to require medical treatment.

This chapter will review the various causes of pain and briefly describe the common treatments used to control pain. In addition, it will discuss the types of medical practices involved in pain treatment and the barriers that prevent some patients from receiving effective pain control.

Pain Signal Transmission

What is pain? The most commonly used definition of pain is "any sensation the patient perceives to be uncomfortable." By this definition, things like anxiety, depression, insomnia, and hunger would all be considered painful, and in some ways they are. What we normally consider pain, however, is any of several different unpleasant sensations that (in theory) serve to warn us that some part of our body is being damaged.

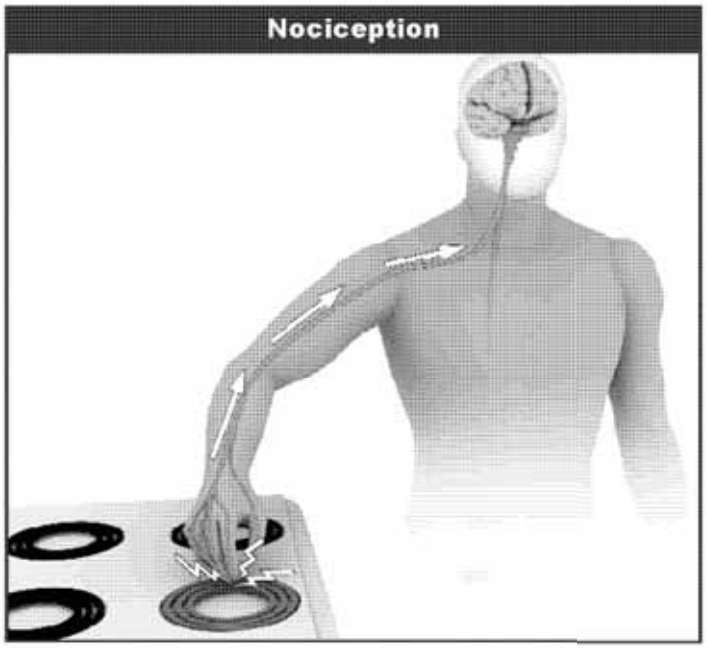
This section describes the origin, transmission, and modification of pain signals, including:

- Nociception
- Transmitting the Pain Sensation to the Spinal Cord
- Connections in the Spinal Cord and Brain
- The Descending Pathways

Nociception

Medically, the pain sensation itself is referred to as nociception (pronounced 'noe-sis-sep-tion'; 'noci' refers to pain). The sensation may lead to some secondary symptoms such as anxiety, nausea, or sweating that add to the discomfort.

Figure 1-1



Nociception begins when a sensory nerve ending in some part of the body is strongly stimulated and sends an electrical signal. These nerve endings normally do not send any signals, but if they are disturbed by a mechanical, thermal or chemical force that might damage the body, they begin actively sending repetitive electrical signals to the spinal cord. The pain sensing nerves function much like a smoke detector in a house: most of the time they are quiet and don't create any "noise", but when activated, they fire off a strong electrical signal to warn the brain of a possible problem.

Transmitting the Pain Sensation to the Spinal Cord

The pain signal travels from the nerve cell (neuron) ending to the spinal cord along a single fiber that is a long branch (also called an axon) off the cell body. Although each individual fiber is microscopically small in diameter, it is long enough to reach from the spinal cord to whatever part of the body that nerve monitors. Every part of the body sends pain signals along thousands of different nerve fibers, which differ in size and structure. The two most important types of pain-transmitting fibers are called C-fibers and A-delta fibers. A-delta fibers transmit the pain signal very rapidly, because their fiber (axon) is covered with a special insulation called myelin that speeds up conduction. C-fibers lack this covering and transmit their signals more slowly. The slow C-fibers transmit at about 1.5 to 6 feet per second, whereas the A-delta signal can travel 40 to 90 feet per second.

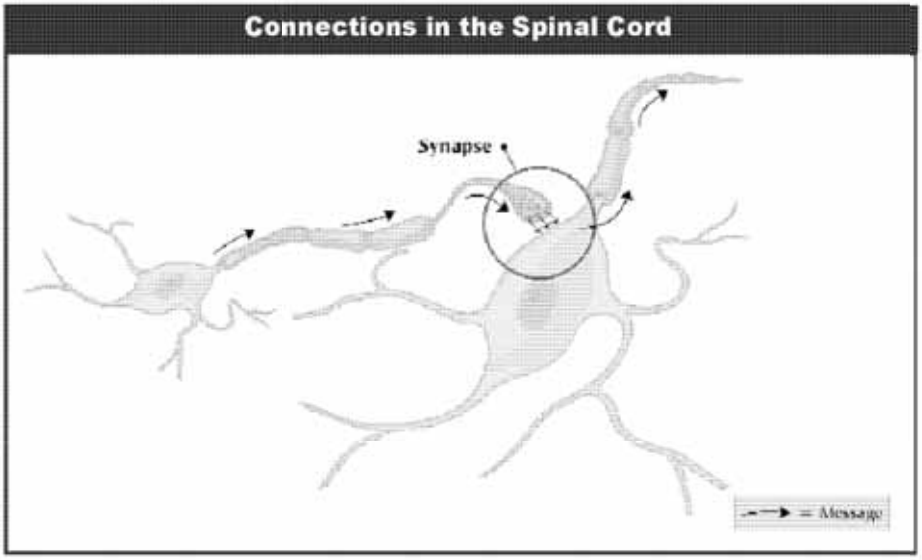
This speed difference is significant enough so that most people can clearly sense the separate pain sensations carried by A-delta versus C-fibers. The fast-conducting A-delta messages arrive first after an injury. This pain typically feels sharper and

"brighter". The C-fibers' message comes a second or so later, and tends to feel more dull, throbbing, and aching. For example, if you've ever hit your thumb with a hammer, you may remember an immediate, sharp pain that in a second or two gave way to a deeper, throbbing pain.

Connections in the Spinal Cord and Brain

An individual pain nerve fiber does not transmit its signal all the way to the brain, but instead connects to a group of second neurons just outside the spinal cord. At the connection between the neurons (which is actually a small gap between the two neurons called a synapse; pronounced "sin-aps"), the sensory neuron releases a small burst of chemical messengers (neurotransmitters) that drift across the gap and bind to special receptors located on the second neuron.

Figure 1-2

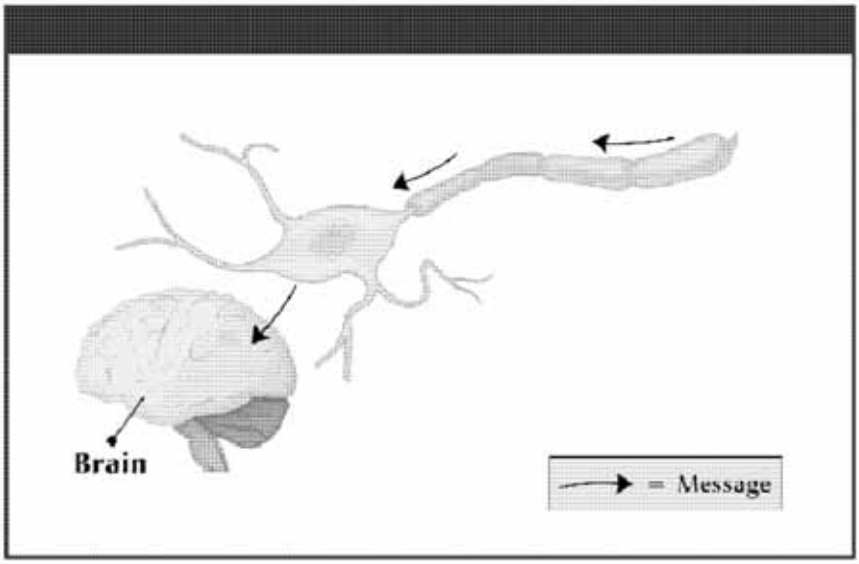


The chemical messenger does not necessarily cause the second neuron to send a signal. Some connections (which are called excitatory synapses) make the second neuron more likely to send a signal, whereas others (called inhibitory synapses) make the second neuron less likely to send a signal. The second neuron is simultaneously receiving signals from dozens or hundreds of peripheral nerves, and the overall sum of the stimulating and inhibiting input determines whether the second neuron will send a signal up the spinal cord.

These secondary neurons send fibers up the spinal cord in large bundles called tracts. The nerve fibers eventually connect to a third set of neurons located in the brainstem. From there the pain message is transmitted to the conscious brain (where we actually

perceive it), to the midbrain (where it activates motivation and the emotional response center), and to parts of the unconscious brain that control bodily functions like blood pressure and sweating. Still other branches carry the pain message to parts of the brain that can modify the pain response.

Figure 1-3



The Descending Pathways

This last set of neurons, the ones that modify the pain response, are of particular interest to us. These neurons send fibers (known as the "descending pathways") back down the spinal cord, giving off branches to the same neurons that originally received the pain input from the sensory nerves. Chemical messengers from these descending fibers inhibit the transmission of ongoing incoming pain signals, reducing these pain signals before they enter the spinal cord to be transmitted to the brain.

The neurotransmitters (chemical messengers) from these pain-inhibiting neurons (descending fibers) chemically resemble opioids such as morphine. The pain-relieving effects of opioids, such as morphine, occur largely because the opioids bind to the receptors of the excitatory neurons (the neurons that first transmit the pain signal), making it less likely that they will send a pain message.

Types of Pain

There are many different types of pain, each of which is a slightly different sensation. For example, stomach cramps and a toothache are both causes of pain, but those two types of pain feel very different. Doctors classify pain into several broad categories to better understand what is causing it and more importantly how to treat it.

One way to separate the types of pain is by location. From a medical standpoint, however, it is more helpful to separate pain according to the kind of organ or tissue that the pain originates from and the type of nerves involved in carrying the pain message. This classification also provides a useful way to think about response to opioids and other pain medications. Such a classification divides pain into the following types:

- Somatic Pain
- Visceral Pain
- Neuropathic Pain
- Central Pain

Somatic (soe-mat-ick) Pain

Somatic pain originates from the skin, muscles, tendons, ligaments, and bones. These parts of the body are well monitored by the brain because they are so important to how we function every minute. One can easily pinpoint the exact location of somatic pain: when you cut your finger with a knife, you do not have to look for the blood to know exactly which finger has been cut. Somatic pain is often sharp, stabbing, throbbing, or aching in nature. Although somatic pain can be severe, it tends to respond well to treatment with opioids.

Visceral (vis-sur-ull) Pain

The body's internal organs, such as the liver, intestines, and stomach, generate visceral pain. In many diseases, somatic pain and visceral pain exist together, as when a tumor begins in an internal organ and then metastasizes to a bone. In contrast with somatic pain, visceral pain tends to be poorly localized and more likely to generate referred pain that is felt some distance away from the actual problem. For example, the pain of angina, which originates in the heart, often radiates to the arm or jaw. This can make the diagnosis of the cause of visceral pain difficult and frustrating

for both clinicians and patients. Opioids are not as effective for visceral pain as they are for somatic pain, although they do provide some relief.

Neuropathic (new-roe-path-ick) pain

Neuropathic pain results when the nerves themselves are damaged. This may happen when a tumor invades a nerve, when a ruptured spinal disk presses on a nerve, or when a nerve is injured. Neuropathic pain is typically burning in nature, although it may also be aching or cause an electric shock sensation. The area involved in neuropathic pain often has allodynia (pronounced "al-oh-din-ee-ah", meaning hypersensitivity) to even light touch.

There are two broad categories of neuropathic pain involving the peripheral nerves. The first type, which involves injury to a single nerve, is termed "neuralgic". The second type is caused by certain diseases, such as diabetes, that damage nerves throughout the body. The longest nerves are the most severely affected, so the pain is most severe in the hands and feet. This type of neuropathic pain is called "peripheral neuropathy". For unknown reasons, opioid medications are often rather ineffective for treating neuropathic pain.

Central pain

Central pain is pain that results from injury, stroke, malignancy, or other lesion in the spinal cord or brain. It is often quite severe, yet unique in that the patient is often unable to describe it and often cannot even describe where the pain is. This leads to frustration for the patient and can be confusing to the health care provider. The pain can affect a large area or may be localized. An increased sensitivity to touch or pain may be present (hyperalgesia or allodynia). The key to the diagnosis of this type of pain is the history of a stroke, injury, or other lesion of the spinal cord or brain in a patient with vague and unusual descriptions of intense discomfort. Treatment of this type of pain is difficult. Lidocaine is often effective, but has to be given intravenously, limiting its usefulness. Tricyclic antidepressant drugs may be useful, but opioids are often not helpful in relieving the pain.

Goals of Pain Management

Pain management is simply reducing a person's pain to a tolerable level that allows the person to function as normally as possible. It is the primary treatment available when curing the underlying disease or condition is not possible. All clinicians practice pain management, at least occasionally. However, a growing number of clinicians either specialize in pain management or dedicate a significant portion of their practice time to pain management.

Obviously, reducing the patient's level of pain is the primary goal of pain management. It should be kept in mind that complete pain relief is often not possible or can only be obtained temporarily. However, a dramatic reduction in pain is almost always obtainable. The pain management clinician or team will have slightly different goals depending on the patient's specific type of condition. Pain management can be divided into 3 types based on the type of pain:

- Acute Pain Management
- Cancer Pain Management
- Chronic Benign Pain Management

Acute Pain Management

The goals in acute pain management are to provide the patient with effective pain relief that allows them to rest comfortably and to rehabilitate after their surgery or injury. Because this type of pain often waxes and wanes over time, short-acting PRN (as-needed) medications may be appropriate.

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Cancer Pain Management

The World Health Organization recommendations for pain management, referred to as the pain ladder, suggests starting with nonsteroidal anti-inflammatory drugs then to weaker and finally, stronger opioids as needed to control pain. The recommendation included as-needed medications to manage break-through pain. Over the years, the efficacy of this approach has been questioned, and some experts have suggested that it is more appropriate to start with opioids (specifically morphine) in patients with more severe pain. (Ventafridda 1987, Zech 1995, Maltoni 2005)

The goal of cancer pain treatment is to provide long-term, effective control of the patient's symptoms. Treatment should be adjusted so that the patient remains alert and largely free of side effects, able to enjoy life.

During the course of their disease, cancer patients may develop depression, insomnia, and anxiety. All of these symptoms can be worsened by uncontrolled pain, which adds to the importance of pain control. It is important, however, to realize that depression, insomnia and anxiety can also worsen the patient's perception of their physical pain. Treatment with specific medications (usually referred to as "adjunctive medications") to address these problems may help reduce the patient's pain significantly. Unfortunately, many patients do not volunteer that they have these symptoms, leading the clinician to incorrectly conclude that the opioid medication is not working effectively, when actually the patient needs an adjunctive medication, a change of dosage, or a change in therapy.

Because cancer pain may require long-term treatment with opioid medications, many patients will eventually develop tolerance to and dependence on opioids. Tolerance refers to the need for increased doses of the medication to achieve the desired pain relief. Physical dependence is a condition that takes place when the body gets so used to having a drug in the system that it experiences symptoms of withdrawal if the person abruptly stops taking the drug or suddenly takes a lower dose. Many clinicians fear the development of tolerance and dependence so much that they do not provide sufficient doses of opioids during the early stages of treatment, hoping that this will prevent the patient from developing tolerance too quickly. In reality, although tolerance and dependence do often occur late in the treatment of cancer pain, they rarely prevent effective pain relief. Undertreatment of pain results in patients with a very poor quality of life and may lead to feelings of hopelessness and despondency.

Whereas undertreatment is the most common problem in cancer pain control, a few patients are overtreated with opioids. This may result in excessive side effects, such as somnolence, that can leave the patient unable to enjoy their life. The primary goal of cancer pain management is to relieve the patient's pain without such disabling side effects.

In summary, the goal of cancer pain treatment is to provide long-term, effective control of the patient's symptoms. Treatment should be adjusted so that the patient remains alert and largely free of side effects and able to enjoy life as much as possible. Unfortunately, these goals are not achieved for a substantial proportion of patients with cancer pain. Despite widespread educational efforts by the National

Cancer Institute, the World Health Organization, and other groups, many clinicians are still not entirely familiar with the correct principles of cancer pain management. Undertreatment of cancer pain and failure to treat associated symptoms with adjunctive medications remain a widespread problem.

Chronic Benign Pain Management

Chronic benign pain refers to pain caused by diseases or conditions that are neither fatal nor completely curable. There are thousands of causes of chronic benign pain; some common examples include

The goal of chronic benign pain treatment is to restore the patient to the highest degree of

- Rheumatoid arthritis
- Traumatic nerve injury
- Migraine headaches
- Chronic back pain
- Endometriosis
- Diabetic neuropathy
- Lupus erythematosus
- Sickle cell anemia

The goals of treating chronic benign pain vary depending on several factors including the temporal (over time) course of the patient's pain, the general type of pain (as discussed in the preceding section) associated with the condition, the patient's functional status, and the presence of associated factors. Some conditions, such as migraine headaches, cause only intermittent episodes of pain and can therefore be treated with short-acting opioids. Most chronic conditions cause some degree of constant pain, however, and are best treated with long-acting or sustained release opioids. Other conditions, such as those involving neuropathic pain, may be treated entirely without opioids.

Many patients with chronic benign pain are candidates for long-acting or sustained release opioid therapy. These patients are very likely to suffer depression, anxiety, and insomnia. However, significant differences exist between the treatment of chronic benign pain and that of cancer pain; therefore, these symptoms may be reated differently.

Patients with chronic benign pain are expected to have a near normal life expectancy; therefore, they will take medications for a longer period of time than some cancer patients. Their condition is not considered terminal, so the primary emphasis of management is on restoring the patient's ability to function. Controlling subjective symptoms is a secondary goal. For example, it may be acceptable for a cancer patient to sleep for 16 hours a day if he or she gets excellent pain relief. The same situation

would not be acceptable for a patient with chronic benign pain who needs to maintain gainful employment.

In addition, the diagnosis of most benign conditions depends on the patient's description of symptoms. A clinician can usually order tests to actually "see" a tumor, but there is no test to "see" a headache. The clinician depends on the patient's description of symptoms to make the diagnosis. Because of this, clinicians are always aware that some patients who want treatment for a chronic benign pain condition may not actually have that condition. Some of these patients may be actively seeking drugs for abuse or resale. Others may have significant psychological problems that lead them to seek medical care inappropriately.

Finally, many chronic benign pain conditions can be treated with a number of therapies, such as nerve blocks or physical therapy, either in addition to, or instead of, treatment with opioids. Some conditions respond very well to such therapies; others respond poorly.

These factors lead to a wide variation in how different clinicians and pain management practices treat patients with chronic benign pain. Some practices rely largely, or even entirely, on nonopioid therapies to treat chronic benign pain. In other practices, most patients receive long-acting opioid medications. This variation depends upon geographic location (some areas of the country still do not readily accept chronic opioid therapy for chronic benign pain), the individual clinician's training or background, and the type of patients seen in that practice.

In general, however, the goal of chronic benign pain treatment is to restore the patient to the highest degree of function possible. Because of the lifelong nature of the condition, high priority is given to avoiding side effects when possible and managing unavoidable side effects, such as constipation.

Pain Management Practitioners

You can communicate with a clinician about pain management much more effectively if you are aware of the perspectives the individual practitioner has before you call on him or her. Each specialist involved in treating pain has different training, perspectives, and techniques to offer. Perhaps the most obvious difference is the techniques each specialist is most likely to use. Most anesthesiologists, for example,

use nerve blocks in their practice quite frequently, whereas fewer non-anesthesiologist clinicians are trained to do those procedures.

The type of therapy the clinician normally uses will also differ depending on the type of condition he/she is treating. Cancer patients are usually treated primarily with opioids, and often with additional medications. Patients with chronic benign pain may be treated through several different therapies including psychotherapy, physical rehabilitation, nerve blocks, acupuncture, and medications.

A few psychiatrists, neurosurgeons, and orthopedic surgeons also specialize in pain management. The practice of oncologists and rheumatologists usually involves some pain management as part of their treatment of cancer and rheumatology patients, respectively. A newer specialty, known as palliative care, focuses on the treatment of patients near the end of life and in hospice settings. Palliative care clinicians come from several disciplines, including family practice and internal medicine.

Currently, subspecialty board certification for pain management is available for anesthesiologists, physical medicine, rehabilitation clinicians, and neurologists. Such clinicians often state that they are "fellowship trained", meaning that they completed a year or more of training specifically in pain management after completing a residency in their specialty.

Credentialing is available through the American Academy of Pain Management (AAPM) as well as the American Academy of Pain Medicine offering designations as a Diplomate, Fellow, or Clinical Associate. The credentialing for all levels requires at least two years of experience working with people in pain and a passing score on the AAPM credentialing test. The level of credentialing is based on education in a healthcare field, but not fellowship training. If these requirements are met, the credential of Diplomate is awarded to those who have a doctorate degree, a designation of Fellow is awarded if the individual has a master's degree, and a Clinical Associate designation is awarded to individuals with a bachelor's degree (or equivalent).

Clinician specialties involved in pain management

Anesthesiologists are commonly consulted to assist in the management of chronic benign pain patients. Many anesthesiologists limit their pain practice almost entirely to performing nerve blocks. Some only perform nerve blocks ordered by other practitioners and after the nerve block is complete, the patients return to the original

practitioner for follow-up care and medical management. Most anesthesiologists who specialize in pain management, however, offer a more complete therapy and follow-up care, including opioid and nonopioid medications.

Physical Medicine and Rehabilitation Clinicians are the fastest growing group of pain management clinicians. In addition to supervising physical therapy, these clinicians may also perform nerve blocks and most offer long-term medication therapy.

Medical Oncologists specialize in the diagnosis, assessment, and treatment of cancer. Some, but not all, oncologists have extensive experience in treating cancer pain. Most are comfortable with prescribing long-term opioid medications but may refer the patient to other clinicians when additional pain management techniques are needed. For most cancer patients with advanced disease, the medical oncologist functions as a primary care clinician and coordinates care until the patient dies.

Neurosurgeons provide surgical treatment of neurologic conditions that cause pain. They may also perform pain-relieving surgical procedures (such as spinal cord stimulation or implantation of medication pumps) in patients who have not had adequate relief of pain with other interventions

Psychiatrists can assist in the management of patients who are also suffering from psychoses, depression, anxiety, or confusion. They also provide supportive psychotherapy to help patients cope emotionally with pain. Psychiatrists involved in pain management have the option of obtaining subspecialty certification in pain management through the American Board of Psychiatry.

Palliative Care Clinicians generally provide end-of-life care to patients who are in hospice or who have terminal conditions. They generally prescribe opioid analgesics and other medication therapy and follow patients through a home health agency or hospice.

Radiation Therapists may be eventually involved in the treatment of cancer patients with advanced disease. The radiation therapist administers radiation treatment that can lead to invaluable relief of the pain due to bone metastasis or tumor growth. A few radiation therapists are also actively involved in cancer pain management and palliative care, but most limit their practice to administering radiation therapy.

General Surgeons and Orthopedic Surgeons provide treatment of medical and orthopedic diseases that can be corrected surgically. They generally provide acute

pain management in the immediate pre- and post-operative period. Orthopedic surgeons may be involved in the management of chronic arthritis pain or back pain, but often refer such patients to their primary care physician or a pain specialist.

Primary Care Physicians are increasingly more willing to provide pain management and prescribe opioids. Although some family physicians have at least basic training in pain management techniques, many do not. In direct contrast with pain specialists, family physicians usually only care for a small number of chronic pain patients at any time. It should not be surprising, therefore, that family physicians may report difficulties with managing both chronic benign and cancer pain patients.

Rheumatologists specialize in treating arthritis, rhematologic, and musculoskeletal disease. These diseases are often associated with chronic benign pain and part of patient disease management is management of the pain symptoms.

Internal Medicine Physicians provide primary care services to a wide range of adult patients. They treat many common illnesses and ailments, including problems such as chronic back pain. Internal medicine physicians may also opt for additional certification in subspecialty fields, such as palliative medicine or rehabilitation medicine.

Nonphysician specialties involved in pain management

Most licensed **nurses**, including nurse practitioners, have daily contact with patients in pain and play a valuable role in the administration of medications for pain relief. In many states, nurse practitioners are allowed to prescribe all schedule II medications. Nurses spend more time with patients than do any other health professionals, thus nurses' assessments of the adequacy of pain control measures and the incidence of drug side effects are extremely important. Other members of nursing staff, such as medical assistants, also provide valuable services in caring for pain patients and communicating information on response to pain medication and adverse effects of medication.

Home care or community nurses play a key role in managing pain patients at home or in hospice. They are sources of advice and information for patients and their treating clinicians and also provide general nursing care, psychosocial support, and symptom management to the patient.

Similarly, office nurses assume an important role in terms of assessment of a medication's effects on the patient's symptoms and quality of life. The physician's

opinion of a medication's effectiveness often is greatly influenced by the reports he or she receives from the office nurse.

Pharmacists, of course, dispense medications for pain patients. They also provide information about drugs to the clinician and the patient. The pharmacist may be the first person to recognize that a patient is over- or under-using his or her medication on the basis of the frequency of prescription refills. Most multidisciplinary pain centers include a pharmacist as a member of the treatment team.

Physician Assistants

Therapists provide an important adjunct in pain management, particularly in situations where movement provokes pain. They can be particularly helpful in the management of patients with back or muscle problems that are causing pain.

Chaplains and Clergy provide support for the patient and the family as they face difficult spiritual and psychological issues and may also help patients resolve guilt, fears, anger, and doubts. These members of the health care team are predominantly used in hospice and palliative care settings.

Psychologists provide counseling and teach relaxation techniques and stress management skills that help patients cope with their pain more effectively. They also work with family members, who often have trouble coping with their loved one's pain.

Alternative Medicine

Biofeedback monitors measure galvanic skin response, hemodynamic changes, and body temperature to increase patient awareness of and control over physiologic processes (such as muscle tension) that may contribute to pain.

Acupuncturists and Massage Therapists may also be useful in select patients. These therapies offer temporary relief of pain to many patients with somatic pain.

Interdisciplinary Team Approach

The interdisciplinary (often called multidisciplinary) team approach to pain management has been a widely accepted standard of pain treatment for decades. As previously mentioned , each type of medical specialist has expertise in certain pain treatment techniques and experience with certain types of patients. It has been recognized since the 1950s that the complex nature of pain management demands the efforts of a team of specialists if the best results are to be obtained.

A multidisciplinary team (Table 1-1) brings many diverse diagnostic and therapeutic skills to the management of a patient's pain. The composition of the team, which will vary from one pain treatment center to another, reflects a growing appreciation of the importance of treating the "whole patient" rather than just the primary symptom. The ultimate aim of the pain management team is to provide rational, integrated, and consistently effective care for every patient.

Table 1-1

The Interdisciplinary Pain Management Team

Patient and family members

Physicians:

- Anesthesiologist
- Physical Medicine and Rehabilitation Specialist
- Medical Oncologist
- Neurosurgeon, Neurologist
- Psychiatrist
- Palliative Care Specialist
- Radiation Therapist
- General Surgeon, Orthopedic Surgeon
- Primary Care Physician

Nonphysicians:

- Nurses (office, hospital, hospice, home care)
- Pharmacist
- Physical, Occupational Therapist
- Chaplain and Clergy
- Psychologist, Counselor, Social Worker
- Massage Therapist
- Acupuncturist

The physical location and makeup of the multidisciplinary team can vary considerably. Medical universities and large hospitals may have very large pain clinics or pain centers with dozens of clinicians and other health care professionals. Smaller pain clinics may have only 3 or 4 clinicians and a dozen or so employees.

Not every patient with pain requires the services of a multidisciplinary team. In some cases, a solo practitioner may be comfortable managing a pain patient. For example,

many oncologists manage pain quite effectively for most of their patients without needing the input of an entire team of specialists. Only those patients who do not get relief through a routine pain treatment protocol are referred to a specialist or multidisciplinary center. As a simple guide, a patient may be considered suitable for referral to a pain clinic or pain center when:

- Pain has persisted for more than six weeks despite attempts to manage the pain with oral medications.
- All appropriate diagnostic investigations have been conducted.
- The recommended treatment of the underlying condition has been shown to be ineffective in that patient.

Pain clinics work with patients who have pain problems that cannot be cured or managed adequately by individual health care professionals offering routine pain management. The pain clinic provides the patient access to clinicians and staff with experience and a variety of approaches to pain management that other medical providers cannot offer. A patient who is referred to a pain center will be adequately assessed and appropriately counseled about the potential benefits and limitations of the available treatment options. After the initial assessment, if the team feels the patient may benefit, the patient can be treated by the specific members of the pain management team who are most likely to be able to provide effective treatment.

The patient will at least be adequately assessed, appropriately counseled and treated. Pain clinics also facilitate the referral of patients to the specific members of the pain management team who are most likely to provide effective therapy.

Current Practice Patterns

Even though a multidisciplinary team is the ideal way to manage a patient with a difficult pain problem, actually organizing and maintaining such a practice can be difficult. Many managed care plans will not reimburse more than one clinician for treating the same patient. In other cases, the patient's insurance may allow certain specialties to bill for pain management, whereas others cannot. For these and other reasons, many pain treatment clinicians remain in solo or small group practice, despite the theoretic advantages of the multidisciplinary team. In such cases, the clinicians often maintain a multidisciplinary approach by referring the patient within a small group of individual consultants from different specialties, all of whom are involved in pain management.

Chronic Benign Pain

Several factors have influenced practice patterns in pain management over the last several years. Reimbursement changes made in 2000 and 2002 have had a dramatic effect on physicians who treat chronic benign pain. These changes have led many physicians, particularly anesthesiologists, to no longer accept patients for chronic medication maintenance. Some pain centers only accept patients for a 90- or 120-day "diagnosis and treatment evaluation", after which the patient must find a primary care provider willing to write prescriptions for his or her medications. Almost half of all pain centers no longer accept any Medicare or Medicaid. Further reimbursement cuts instituted in 2007 are likely to lead to further cutbacks in care available for these patients.

Many pain treatment physicians who perform procedures such as surgery or nerve blocks now focus on those procedures because they are reimbursed at much higher rates than are office visits. In some cases, this has resulted in fragmenting of pain centers with the "invasive" physicians practicing separately from the "medication" physicians. For the same reasons, some primary care and palliative care physicians now provide medical management and chronic opioid prescriptions to chronic benign pain patients, simply because pain specialists are not willing to do so.

Beginning in 1999, the diversion and abuse of opioids, particularly OxyContin®, led to a widespread focus of attention on prescription drugs. Federal and local drug enforcement agencies arrested many physicians who had participated in drug diversion and some who simply overprescribed opioids or kept poor records of the prescriptions and pain patient's diagnosis and response to therapy. In reaction, many physicians have become reluctant to prescribe opioids for medical problems other than acute and cancer pain. Most, however, continue to prescribe opioids when they are indicated, although they exercise greater caution to prevent diversion.

Cancer Pain

Cancer pain can be the result of the disease process itself or from the treatment for the disease. About two-thirds of patients with bone metastases have severe, debilitating pain. Of these, about a fourth continue to have pain despite analgesic therapy. Pain from the effects of the disease on the viscera as well as pain from the treatment of the disease (scarring, neuropathic pain, radiation injury) is also common.

As many as 60% of cancer patients have inadequately controlled pain, yet opioid therapy, given in conjunction with dose titration and frequent assessment, offers pain control in up to 90% of patients. (Cleeland 2005, Koizumi 2004) Despite the availability of effective pain medications and pain management guidelines, a number of studies have demonstrated that cancer pain remains undertreated. Barriers to adequate treatment include physician under-estimation of patient's pain, inadequate assessment, and a reluctance on the part of patients to report pain. (Gralow J 2007, Shaiova 2006)

Palliative Care and Hospice Care

Cancer pain management can be divided into 1) management during active anticancer therapy, which is usually handled by the treating oncologist, and 2) end-of-life pain management. End-of-life care has increasingly become managed by palliative care clinicians who work through hospice agencies. Although some hospices are actual buildings, most are home health agencies that provide terminal care to the patient at home.

According to the National Association for Home Care and Hospice, there were 3078 active hospice programs in the United States. More than 894,000 Medicare beneficiaries receive hospice care each year, 43% of whom have cancer. However, it is not necessary to have cancer to receive hospice care; anyone with a terminal illness is eligible.

There are three generic criteria for admission of terminally ill patients to hospice:

- Completion of all active curative treatment.
- Patient's awareness of the terminal nature of his or her condition.
- Patient and family's clear understanding of the goals of hospice care.

Medicare also requires that the person have a life expectancy of approximately six months or less. However, 15% of hospice patients live longer than six months.

Hospice agencies provide complete symptom management, but do not provide any curative treatments. Cost-effective treatment is extremely important to hospice providers, because Medicare pays the hospice organization a per diem of approximately $118 for every day the patient spends in home-based hospice care. The hospice organization is responsible for paying all of the patient's expenses from that amount, including hospital bills, lab tests, clinician's visits, and medications. For

this reason, hospice providers and palliative care clinicians attempt to use long-acting or sustained release oral opioids whenever possible and avoid more expensive intravenous medication.

Barriers to Effective Pain Control

Despite the improvements in pain management that have occurred over the past decade, several barriers to effective pain control remain:

- Fear of addiction
- Lack of education about pain and pain control
- Opioid phobia
- Fear of legal or regulatory action

Fear of Addiction

Fear of addiction to opioids remains a major obstacle to effective treatment for pain. Unfortunately, few clinicians and even fewer patients understand exactly what addiction (which is more properly termed "substance abuse") is. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders defines substance abuse as "a maladaptive pattern of use of a chemical substance that significantly interferes with the person's life". It is important to recognize that tolerance and dependence (discussed above) do not indicate addiction. Rather, they are an expected consequence of taking opioids in

Table 1-2

Signs Associated with Substance Abuse

- Repeated requests for short-acting medications (e.g. a short-acting opioid in tablet-form that is chewed or broken).
- Repeated requests for early refills, especially when the patient has "typical" excuses such as "the pills fell in the toilet", "the dog ate them*", "someone stole my medicine".
- Frequent telephone calls, particularly after hours or on weekends.
- Frequent requests to change medication because of side effects or lack of efficacy.
- More than a single incidence of other physicians prescribing opioids.
- Past history or family history of substance or alcohol abuse.
- History of preexisting psychiatric illness, especially bipolar disorder, schizophrenia, or personality disorder.
- Social history of dysfunctional or high-risk behaviors including multiple arrests, multiple marriages, abusive relationships, etc.

* unless the dog is very large, eating a bottle of prescription opioids should result in the pet's untimely demise.

moderate to high doses for a significant length of time.

Proper use of opioids is not "maladaptive" nor does it "interfere with the person's life"; instead, it allows the patient to return to a functional life. However, some chronic pain patients do have a substance abuse problem (Table 1-2).

The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of "pseudoaddiction". Pseudoaddiction is a set of behaviors (Table 1-3) that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.

Lack of Education about Pain and Pain Control

In their medical training, doctors typically receive only a few lectures on the subject of pain management. Many practitioners are therefore not comfortable with assessing pain complaints and prescribing the proper treatment. Some of the areas in which misunderstandings about the evaluation and management of chronic pain commonly occur are pain assessment and underuse and underdosing of opioids.

Pain Assessment

Pain is a subjective experience that may or may not correlate with the observer's perception of underlying pathology. It is not unusual for clinicians to minimize a patient's pain complaints and therefore prescribe inadequate amounts of opioids. Pain assessment instruments such as the visual analog or verbal rating scales may help patients to communicate the presence and severity of pain. Information about the characteristics of pain (i.e., pain location and quality, temporal pattern of the pain, and response to any previous treatment) may also help to refine treatment. (Berry 2000) The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has issued pain assessment recommendations that include performing an initial pain screening assessment, a more comprehensive pain assessment if pain is identified, and collection of data to monitor the appropriateness and effectiveness of pain management. A visual analog scale is often used to accomplish this task.

Underuse and Underdosing of Opioids

Oral administration of opioids often fails because the patient is not given a high enough dose of medication. This is quite likely to occur when the patient is switched from intramuscular or intravenous routes to the oral route or when a different opioid is substituted. Clinicians should refer to equianalgesic charts and titrate the dose to

the individual patient. Clinicians can also consult pharmacists for advice regarding changing opioids and determining equianalgesic dosing.

Opioid Phobia

An irrational fear of using opioid analgesics is a fairly common cause of undertreatment of pain. Opioid phobia can be exhibited by patients, their families, health care professionals, legislative and regulatory agencies, governments, healthcare insurers, and societies as a whole. Its end result is unavailability and underutilization of opioids, and its victim is the inadequately treated patient with pain.

Fear of Legal or Regulatory Action

Since 1999, government agencies and state medical boards have arrested and disciplined doctors with increasing frequency for improper prescribing. The vast majority of these actions have involved criminal selling of prescriptions by doctors or overprescribing of massive amounts of controlled substances without proper documentation. Unfortunately, many ethical clinicians have become fearful of prescribing opioids after learning of these incidents.

In reality, regulatory agencies have focused on those drugs with the highest diversion potential and street value. In the 2005 Drug Abuse Warning Network (DAWN) report, hydrocodone, oxycodone, and methadone were the most frequently abused prescription opioids. (US Depart. of Health and Human Services 2005)

NOTE: Any opioid can be abused in an individual case, and you should never state that one opioid is "safer" or "less abusable" than others. It is more appropriate to quote current data on the frequency of abuse or the street value of the different opioids, which corresponds with the demand for diversion of that product. For example, at the time that this manual was prepared, oxycodone and hydromorphone had very high street values, whereas time-release morphine preparations had very low street values. Current statistics are maintained on the web pages of the National Institute on Drug Abuse (www.nida.nih.gov), the Drug Enforcement Agency (www.dea.gov), and the National Criminal Justice Reference Service (www.ncjrs.gov).

Summary

Pain is a primary symptom of many different diseases. The treatment of pain can be simple and straightforward or extremely complex. Some patients may be well managed by their primary care clinician, whereas others require the efforts of a team of specialists representing a variety of disciplines. Clinicians that are often involved in pain care include primary care clinicians, palliative care clinicians, oncologists, physical medicine specialists, anesthesiologists, neurologists, nurse practitioners, physician assistants, and surgeons. Additionally, invaluable assistance in the care of these patients may be provided by nurses, physical therapists, psychologists, pharmacists, clergy, acupuncturists, massage therapists, and others.

The type of care the patient receives differs depending on the type of pain (chronic benign or cancer), the cause of pain, and other factors, such as the presence of depression, whether the pain is visceral, somatic, or central and whether the pain is acute or chronic. Other factors include: home life, social/economic status, etc.

Although some progress has been made in providing good pain control to every patient, many factors still interfere with pain management. These include inadequate education of health care providers, fear of regulatory action by clinicians, and inappropriate fear of addiction.

Resources

American Academy of Pain Management
http://www.aapainmanage.org/

American Academy of Pain Medicine
http://www.painmed.org/

The American Chronic Pain Association
http://www.theacpa.org/

American Pain Foundation
http://www.painfoundation.org/

American Pain Society
http://www.ampainsoc.org/

Pain Balance (Actavis)
www.painbalance.org

National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/disorders/chronic_pain/chronic_pain.htm

National Institute on Drug Abuse
http://www.drugabuse.gov/

American Society for Pain Management Nursing
http://www.aspmn.org/

The American Society of Anesthesiologists
http://www.asahq.org/

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Self-Assessment Test

Circle the best response

1). The medical term for painful sensation is
   a. Neuropathic
   b. Nociception
   c. Viscerosation
   d. Anesthesiologist

2). The nerve fibers that travel from the brain and modify the pain response by secreting neurotransmitters that chemically resemble opioids make up the
   a. Descending pathway
   b. C-fibers
   c. Synapse
   d. Drug Enforcement Circuit

3). There is a consensus among experts that cancer pain can be well controlled in what percent of patients through the use of noninvasive, low-technology approaches?
   a. 8%
   b. 18%
   c. 50%
   d. 80%

4). The primary goal of pain management for chronic benign pain is to restore the patient's
   a. Ability to function
   b. Pain-free state
   c. Home life to normal
   d. Finances

5). Opioid_____is an irrational fear of using opioid analgesics.
   a. Overprescribing
   b. Addiction
   c. Tolerance
   d. Phobia

6). Hospice services are primarily provided at
   a. Major hospitals
   b. Small community based hospitals
   c. Clinician's offices
   d. The patient's home

7). Which of the following statements are TRUE?
   a. Substance abuse may be characterized by "a maladaptive pattern of use of a chemical substance that significantly interferes with the person's life"
   b. Opioid tolerance refers to the need for increased doses of the medication to achieve the desired pain relief.
   c. Opioid dependence means that the patient develops physical dependence and a withdrawal syndrome will develop if the opioid medications are stopped suddenly
   d. All of the above?

8). Which of the following are NOT barriers to effective pain control?
   a. Fear of addiction
   b. Lack of clinician education
   c. Development of tolerance
   d. Fear of regulatory action

9). True or False – Visceral pain arises from muscles, joints, and tendons.
   a. True b. False

10). Neuropathic pain arises from damaged nerves.
   a. True b. False

11). Somatic pain is usually sharp, stabbing, or aching in nature
   a. True b. False

12). Somatic pain responds to opioids better than neuropathic pain does.
   a. True b. False

13). Anesthesiologists make up the majority of pain specialists.
   a. True b. False

14). Most cancer patients receive their pain medication from family practice clinicians.
   a. True b. False

Answers to Self-Assessment Test

1) b	8) c
2) a	9) b
3) d	10) a
4) a	11) a
5) d	12) a
6) d	13) a
7) d	14) b

CHAPTER TWO

Clinical Evaluation of Pain

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the frequency of both chronic benign and cancer pain.
- List at least 6 adverse effects of chronic benign pain.
- Describe the basic steps in the initial assessment of a patient in chronic benign pain.
- Understand the difference between intensity and characteristics of pain.
- Understand the benefits of psychological assessment of patients with chronic benign pain.
- Know the common types of psychological factors that may influence chronic benign pain.
- Understand the indication for performing diagnostic tests in patients with chronic benign pain.
- Understand that ongoing evaluation of treatment is necessary.

Terminology

Inflammation:	Pain, redness and possible swelling due injury or infection.
Pain behaviors:	Exaggeration or magnification of the effects of pain.
Psychological:	Originating from the conscious or subconscious mind.
Physiologic:	Originating from the physical processes of the body.
Neurological:	Originating from the nerves or nervous system.
Socio-environmental:	Originating from, or strongly influenced by, social or environmental pressures.
Somatoform disorders:	Psychological conditions that produce medically unexplainable physical complaints even though there is nothing physically wrong with the patient.
Temporal:	The course of a situation or circumstance over time.

Introduction

Chronic benign pain results not only from the patient's physical problems, but also as a result of the complex emotional factors that the patient and family experience. The key to effectively managing chronic benign pain is a thorough assessment and proper diagnosis. Only when all of the factors contributing to the patient's pain are known can effective treatment be given. This module focuses on the key parts of the chronic benign pain assessment.

- Initial assessment of the pain with a focus on identifying the cause
- Assessing the pain intensity
- Assessing the characteristics of the pain
- Psychosocial assessment
- Past medical history
- Physical examination
- Diagnostic tests
- Evaluation of treatment

The Scope of Chronic Benign Pain

Chronic pain (including both chronic benign pain and cancer pain) is a common, and largely unrecognized problem in American society. Even 20 years ago, chronic benign pain was found to be the country's most costly health problem. The problem has increased since then as the average age of the population has increased. Currently, about 75 million persons suffer from some form of chronic benign pain, and the total costs of chronic benign pain are estimated at 90 billion dollars a year.

About 50% of all hospital patients and 40% of all patients seen in general practice clinics suffer from at least one type of chronic benign pain. Between one-third and one-half of these chronic benign pain sufferers have pain severe enough to require daily medication. Low back pain is the most common cause of disability in persons under 45 years of age and affects more than 8 million Americans.

About 50% of all hospital patients and 40% of all patients seen in general practice clinics suffer from at least one type of chronic pain.

Although the number of persons who suffer from cancer pain is far smaller than the number suffering from chronic benign pain, it still is a big problem. Cancer is diagnosed in about 1 million Americans per year. With the increased length of survival due to modern cancer treatment, almost 10 million persons have a diagnosis of cancer at any one time, and most of them experience some degree of chronic pain.

Unfortunately, the treatment these patients receive is largely using the acute pain model, which is often inadequate for treating chronic benign pain. Chronic pain not only affects bodily functions it also causes anxiety and depression, results in numerous unsuccessful medical interventions, disrupts family lives, and causes financial and social problems for the sufferer. Unlike acute pain, the severity of chronic benign and cancer pain cannot be accurately predicted by observing obvious tissue damage. An individual's perception of pain is a complex phenomenon that involves psychological and emotional processes. Pain perception is a far more complex process than the simple activation of nociceptive (pain-sensing) pathways in the nervous system (see Chapter 1).

For most chronic benign pain patients, the proper treatment of their condition, while rarely curative, can markedly reduce suffering and improve ability to function. However, it must always be remembered that there is no single approach that

effectively treats all types of chronic benign pain. Instead, an individualized pain management plan must take into account the type of disease, characteristics of the pain, concurrent medical problems, and the psychological and cultural characteristics of the patient.

To individualize the patient's therapy, a thorough and complete evaluation of the condition must be made. Failure to properly evaluate the condition results in repetitive, unnecessary tests and procedures, which carry risks for complications and increased medical care costs.

Initial Pain Assessment

The initial assessment should focus on identifying the cause of the pain, which in turn leads to the development of a pain management plan. The initial evaluation of pain should include a detailed history and an assessment of the pain's intensity and characteristics. A physical examination, emphasizing the neurological examination, should be performed. At least a brief psychosocial assessment should be obtained in every patient, with a more in-depth evaluation performed on those with obvious emotional or psychological symptoms. Depending on the information found by the evaluation, further diagnostic tests may be required to determine the cause of the pain.

Attention to detail is important as a delayed or incorrect diagnosis results in increased morbidity and needless pain and suffering. The evaluation should begin by obtaining a complete description of the patient's pain. The following information is needed:

- *Intensity* – How much does it hurt right now? How much does it hurt at its worst? How much does it hurt at its best?
- *Location*- What part of the body hurts?
- *Onset and temporal pattern* – When did the pain start? How often does it occur? Does its intensity change over time?
- *Description* – What words accurately describe the pain?? Does the pain start in one area and travel to another?
- *Aggravating and relieving factors* – What makes the pain better or worse? What other symptoms occur with the pain?
- *Previous treatment* – What types of treatments have you or your health care provider tried in relieving the pain? Have you used any nonprescription methods or medications to relieve the pain? Were any of these

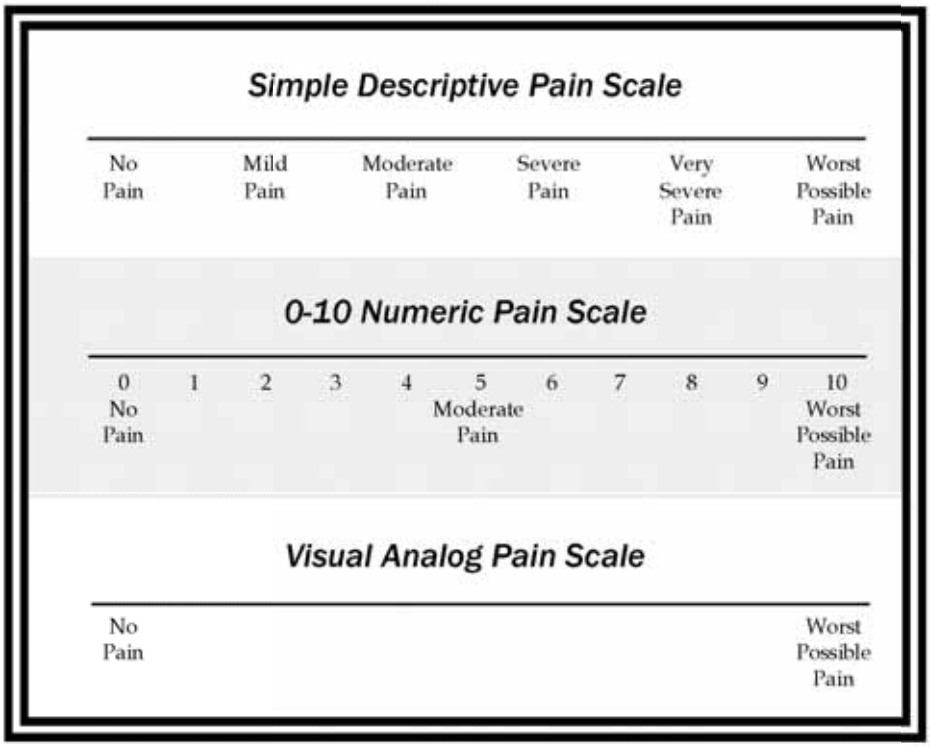
treatments effective?

- *Effects* – How does the pain affect mood, physical function, and social function?

Assessing Pain Intensity

One effective method of assessing pain intensity is to provide the patient with a visual scale, examples of which are shown in Figure 2-1. The patient is asked to grade the intensity of pain on the basis of the scale. Although all of the scales shown in Figure 2-1 are still in use, the Visual Analog Scale (VAS) has been validated and is considered to be the most reliable.

Figure 2-1.



Assessing the Characteristics of the Pain

A complete assessment of acute pain often consists of little more than some form of pain severity score. The cause of pain is usually obvious (e.g., the broken bone or surgical incision), and the severity of pain is usually proportional to the physical damage. The pain assessment simply shows how effective the pain treatment (usually a short-acting opioid) is.

In contrast, chronic benign pain and many cases of cancer pain include physiologic, neurological, psychological, socio-environmental, and learned behavior components. Some patients with chronic pain will have an obvious cause of pain, but simply relieving that physical abnormality (if it is possible) will not completely relieve the patient's pain. This does not in any way mean that the pain is psychological. Most studies indicate that chronic benign pain, no matter what the original cause, eventually causes abnormalities to develop in the nervous system, vascular system, and/or musculature. Over time, these abnormalities will eventually worsen the patient's pain. Even if the source of the original pain is relieved, these secondary abnormalities are sufficient to cause continued pain.

There are physiologic, neurological, psychological, socio-environmental, and learned behavior components in every case of chronic benign

In addition, most persons with chronic benign pain will have some psychological symptoms (depression, anxiety, etc.) in addition to their pain. Many patients, despite their best intentions, will also have unconsciously learned to use their pain to manipulate others to some extent, as a way to avoid unpleasant situations. Over time, family members become focused on the patient and family life begins to revolve around the affected person's pain. These behavior changes can develop in even the most well-intentioned individuals.

For these reasons, the assessment of chronic benign pain is more complex than the assessment of acute pain. Although the severity of chronic benign pain is assessed in the same way as that of acute pain, the severity score alone is not a very useful measurement for chronic benign pain. In acute pain, the measure gives the physician guidance on how much or what type of pain medication to offer the patient. However, with chronic benign pain, saying "Mrs. Smith has had bad pain" is like saying "Mrs. Smith is awake". It is already clear from the context of the situation that the chronic benign pain is severe enough to be a problem for the patient. Documenting change of

pain severity in a patient with chronic benign pain is more useful as an indicator of how effective a given treatment is for that patient.

Whereas it is usually relatively easy to determine the location of pain, assessing the characteristics, or description, of the pain can be quite difficult. Because many patients find it difficult to describe their pain spontaneously, an adjective checklist (Appendix 2-1) is often used to assess the characteristics of a patient's pain. This description of the pain's characteristics may be the most important information obtained during the initial evaluation. For example, burning, hypersensitivity, and electric shock sensations are associated with neuropathic pain, whereas cramping sensations are associated with visceral pain (see Chapter 1). Aching or throbbing pains are characteristic of somatic damage involving muscles, bones, or tendons. The use of certain adjectives, such as "sickening" or "punishing" are associated with significant emotional distress rather than physical problems. Vague or changing descriptions of the area that hurts may indicate that a large emotional component is involved in the patient's perceived pain. Vague symptom description can also occur with central pain syndromes, such as those that develop in some stroke patients (see Chapter 1).

Vague or changing descriptions of the area that hurts may indicate that a large emotional component is involved in the patient's perceived pain.

Also important is the temporal (over time) course of the pain and its association with certain activities. Pain that is worse in the afternoon and evening or worse after activity, for example, may be associated with inflammation of the joints, muscles, and tendons. The combination of the pain's characteristics with its temporal course provides valuable clues concerning the physical source of the pain. Aching, throbbing pain that is worse in the morning and evening may be associated with arthritis and certain muscular diseases. Tingling pain that shoots down the leg with certain movements may indicate compression or damage to the nerves in the lower spine.

Psychosocial Assessment

Patients with cancer, and most patients with chronic benign pain, have real, physical causes for their pain that are due to their cancer or treatment. However, many also have some psychological factors that modify their perception of pain. Certainly, depression and anxiety are to be expected when a person suffers near constant pain, or sudden, unexpected episodes of severe pain.

Between 20% and 25% of cancer patients meet the psychiatric criteria for major depressive syndrome during at least part of their illness. About 20% also report that they suffer anxiety that is severe enough to interfere with their ability to function. The incidence of both problems is even higher in patients with chronic benign pain.

Whether the psychological factors existed before the patient developed chronic benign pain, or only after they become debilitated by their condition, is not important. However, it is extremely important to identify and treat these factors. If they are not identified and treated, relieving the patient's pain may be impossible. Many patients find it difficult to say (or even feel) that they are depressed, lonely, or sad. Such persons may instead simply ask for more pain medication. They may only recognize the pain or may be attempting to relieve their emotional distress by taking advantage of the sedating or euphoric effect of opioids. This may lead the physician to inappropriately increase the medication dosages, potentially leading to excessive side effects.

A formal psychiatric or psychological evaluation is usually not necessary for the evaluation of patients with chronic pain. Many centers will administer a few brief written questionnaires that accurately detect depression and major psychiatric problems. These brief evaluations depend upon the physician's experience to determine which patients need in-depth psychiatric or psychological evaluation.

Formal psychotherapy is rarely required for chronic pain patients, but treatment with medication to relieve depression and anxiety is often necessary. Support groups or individual counseling to help the patient learn new coping skills may also be helpful. Cancer patients, in particular, often benefit from family counseling or group support.

Somatoform Disorders

Although most patients with chronic benign pain experience some psychological symptoms, in a few cases the psychological problems are actually the primary cause of the chronic pain. These psychological conditions are the somatoform disorders, a group of psychological conditions that produce medically unexplainable physical complaints. These patients do not consciously feign or lie about their symptoms; they truly experience the symptoms and therefore believe they have a physical illness. Somatoform patients often "doctor hop" from physician to physician, undergoing a multitude of repetitive diagnostic tests and even exploratory surgery in an attempt to determine a cause for the pain. As many as 5% of the patients evaluated for chronic benign pain actually have somatoform disorders.

Past Medical History

The past medical history can be quite complex in a patient with chronic benign pain. In addition to the usual information, such as past surgeries, medical illness, and family history of illness and allergies, a complete history of the pain problem should be obtained. This must include past efforts to diagnose the problem and a complete listing of those tests. It is important to know which treatments have been tried, both to avoid repeating unsuccessful treatments and failure to respond to certain therapies may provide clues about the nature of the problem.

Physical Examination

The physical examination should include careful examination of all painful sites described by the patient and a complete neurological evaluation. Palpation (feeling and pressing) of the painful area may help the examiner to determine exactly which anatomical structures are involved in the pain process. Moving the patient's major joints or spine may demonstrate damage to these structures or compression of nearby nerves.

Common sites of pain referral should also be evaluated (e.g., shoulder pain may emanate from abdominal sources; knee and hip pain may be referred from lumbar spine lesions). In addition, the patient should be observed for cues that indicate the source of pain, such as distorted posture, impaired mobility, guarding (bracing against or resisting the touch of the examiner) the painful area, or restricted movement of a

limb. The patient should also be observed for signs of anxiety, attention seeking, or depression.

Pain Behaviors

Because pain is subjective, the examiner will use several clues to help determine if the patient is reporting accurately. One type of clue is the presence of "pain behaviors". Pain behaviors are generally considered dysfunctional behaviors and are common in chronic pain patients. During the physical examination, these behaviors manifest as a magnification of symptoms out of proportion to any possible illness, hyperemotional responses, or exaggerated responses to simple questions. Although these behaviors are emotional in nature, they do not usually indicate psychological problems. Rather, they are learned behaviors, which sometimes develop when patients are convinced that people do not believe how severe their pain is or in order to manipulate others. The presence of these behaviors, however, will alert the physician that the patient may not be reporting symptoms or answering questions accurately.

Pain behaviors usually involve magnification of symptoms out of proportion to any possible illness, hyperemotional responses, or

Behavior Consistency

Another factor evaluated during the physical examination is verbal-behavior consistency. This simply means that the patient's actions and words match up. If the patient says, "I'm in agony" while smiling and talking on a cell phone, that's not consistent. Temporal consistency of behavior means that actions do not change inappropriately over time or in different circumstances. If a patient winces, grimaces, and can barely stand when the nurse is in the room but is chatting amiably while waiting for the elevator 5 minutes later, he or she is not exhibiting temporal consistency of behavior.

Finally, the examiner will note the specificity of requests for treatment to identify patients who are drug seeking. "Nothing but Dilaudid will relieve my pain" or "only injectable medicine works on me" are potential signs of drug-seeking patients, but may in fact be a patient being truthful with their healthcare provider, after trying various medications.

Diagnostic Tests

The purpose of diagnostic tests, such as X-rays, CT or MRI scans, and laboratory tests, differs between chronic benign pain patients and cancer patients. In cancer patients, the major purpose is to visualize the spread of tumor (or absence of tumor), which allows the oncologist to determine what treatment, in addition to symptom management, is needed. Diagnostic tests frequently provide invaluable information for cancer patients. In chronic benign pain, however, the major purpose of diagnostic testing is to rule out the presence of any disease for which there is a curative treatment. In most cases, no curable disease will be found, but it is important to be absolutely certain that this is the case. Once all treatable causes of the pain have been eliminated, the pain specialist can begin to manage the patient's symptoms.

Evaluation of Treatment

Once a therapy has been prescribed, the patient's improvement (or lack of improvement) must be monitored. Although this would seem quite simple, in reality it can be rather complex for two reasons: First, pain treatment rarely results in complete and total pain relief, so patients will rarely volunteer that a treatment worked completely. The question becomes "is the pain improved, and is the improvement sufficient?" Numeric or visual analog pain scores are very useful ways to judge improvement.

Secondly, chronic pain, whether from cancer or benign causes, normally waxes and wanes over time. Therefore, it may be difficult to tell whether improvement is from a recently started medication or is just the normal change in pain severity that occurs over time. The use of a "pain diary" in which the patient marks his or her pain level several times each day can be an effective way of determining how much relief is obtained from a given treatment.

When discussing pain assessment and control with patients, members of the health care team should emphasize the importance of a factual report, avoiding either minimizing or exaggerating symptoms. If anxiety or depression is significant, patients should be asked to rate their emotional distress separately from their pain by using similar scales. When discrepancies between behaviors and self-reports of pain occur, these differences should be discussed with the patient and the pain management plan should then be revised.

Clinicians should be aware of the unique needs and circumstances of patients from different age groups or from various ethnic, cultural, and educational backgrounds. Certain cultures have strong beliefs about pain and its management. Members of some cultures may hesitate to report unrelieved pain, whereas others readily complain about even the most minor unrelieved pain.

It is also important to ask the patient about improved ability to function. Some persons will report that their pain level remains high, but when questioned further, it becomes apparent that they are engaging in activities that were not possible before beginning medication. Family members should also be questioned about changes in activity level and any side effects that they may have observed in the patient.

Summary

The first step in the management of chronic benign pain is a comprehensive clinical assessment. By specifically evaluating the pattern and type of pain and diagnosing the likely specific causes of the pain, the clinician is taking a major step toward relieving the patient's discomfort.

The initial evaluation of pain should include a complete history including assessment of the intensity, location, temporal course, and characteristics of the pain. A psychological assessment, physical examination, and a review of diagnostic tests should be done. During the evaluation, the physician should also evaluate the patient for consistency between the patient's behavior and the patient's subjective complaints.

Once treatment has begun, therapy is evaluated by using numerical or visual scales of pain severity. It is also important to ask the patient and family about side effects and whether the patient's functional status has improved.

Self-Assessment Test

Circle the best response

1). What percent of patients seen in a general practice office suffer from some type of chronic pain?
   a. 10%
   b. 20%
   c. 40%
   d. 60%

2). How many persons in the U.S. have cancer at any one time?
   a. 100,000
   b. 1,000,000
   c. 10,000,000
   d. 3,418

3). The cost of chronic pain in the U.S. is about
   a. 9 billion dollars a year
   b. 19 billion dollars a year
   c. 90 billion dollars a year.
   d. 900 billion dollars a year.

4). What percent of cancer patients with pain meet the criteria for major depression?
   a. 10%
   b. 25%
   c. 50%
   d. 75%

5). Is the number above higher or lower for patients with chronic benign pain?

6). Psychological disorders that can cause a patient to experience physical symptoms and pain are called_____.
   a. Somatoform disorders
   b. Obsessive Compulsive disorders
   c. Malingering
   d. Anorexia

7). Pain behaviors are:
   a. The expected symptoms of a person in chronic pain
   b. Repetitive actions likely to cause injury or pain
   c. Exaggeration or magnification of the severity or effects of pain
   d. Changes in family dynamics that revolve around the pain patient

8). Which of the following types of behavior suggests that a patient's pain complaints are valid?
   a. Temporal consistency in behavior in response to pain
   b. Requests for only specific pain medications
   c. Verbal descriptions of pain that are out of proportion to physical findings
   d. All of the above

Answers to Self-Assessment Test

1). c	5). higher
2). c	6). a
3). c	7). c
4). b	8). a

Appendix 2–1

McGill Adjective Checklist for describing pain

Please circle the appropriate number, telling us how severely you experienced the symptom described by each of the following words over the last week. If the symptom does not describe your pain at all, circle 0 (none).

	none	mild	moderate	severe
throbbing	0	1	2	3
shooting	0	1	2	3
stabbing	0	1	2	3
sharp	0	1	2	3
cramping	0	1	2	3
gnawing	0	1	2	3
hot/burning	0	1	2	3
aching	0	1	2	3
heavy	0	1	2	3
tender	0	1	2	3
splitting	0	1	2	3
tiring/exhausting	0	1	2	3
sickening	0	1	2	3
fearful	0	1	2	3
punishing/cruel	0	1	2	3

CHAPTER THREE

Chronic Pain Treatment

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the commonly used pain therapies.
- Explain the basic principles of pain management.
- Describe 3 types of nonopioid analgesics.
- State the difference between opioid agonists, antagonists, and agonist-antagonists.
- Review the most frequently used opioid agents.
- Understand the advantages and disadvantages of each controlled-release opioid preparation.
- Examine the various conditions in which opioids and nonopioids are most commonly used.
- Discuss the use of adjuvant drugs used to augment opioids.
- Understand the principle of dose titration.
- Discuss the use of nonpharmacologic interventions for pain control.

Terminology

Abuse :	The use of a prescription medication in a manner other than that for which it was prescribed. This can include recreational use of a prescription drug.
Acupuncture:	A procedure that originated in Far Eastern medical traditions that involves inserting needles into specific locations of the body to relieve pain and other symptoms. This is different than dry needling and moxibustion.
Adjuvant	Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. The term adjuvant itself means an aid or assistant and the adjuvant drug is typically given as an additional medication to augment pain control.
Adsorption:	A process by which a thin layer of a material is attached to another, as when molecules of medication are attached to beads. This term is similar in spelling, but different in meaning, to the more familiar term, absorption.
Agonist:	a drug that binds with a receptor on a cell and initiates the same reaction or activity produced by the binding of an endogenous substance.
Agonist-antagonist:	Medication that has one effect at low doses and a different effect at higher doses. For example, at low doses, the drug may act as an agonist, but acts as an antagonist at higher doses. Example: Buprenorphine
Analgesic ceiling effect:	Opioid analgesics theoretically have no limit to the analgesic effects mediated by the mu receptor. However, opioids stimulate additional receptors that cause side effects that limit the maximum dose that can be given. For example, while morphine could theoretically be titrated upward indefinitely to control pain, high doses can cause respiratory depression, thus the actual maximum dose that can be given is limited by the risk of respiratory depression (and/or other side effects).
Anatomical pathology:	The actual physical disturbances in the body. For example, a broken leg is the anatomical pathology and leg pain is the symptom.
Anorexia:	Lack of a desire to eat. (The term is similar to 'anorexia nervosa' but these are different medical conditions.)
Antitussive:	Effective at relieving coughing. Anti-tussive effects associated with opioids are due to μ-receptor and possibly κ-receptor stimulation.
Baseline dose:	A dose of pain medication that is given consistently to achieve an acceptable level of pain control in a given patient. The pain control is effective most of the time in most situations but may require supplementation (e.g., the pain relief is effective during both the peaks and troughs of the serum drug levels).

Biliary colic:	Pain due to an obstruction(and subsequent increases in pressure) in the gallbladder or bile collecting system in the liver. This medical condition can be an adverse effect of opioid drugs. A few opioids, such as meperidine, fentanyl, and butorphanol, produce less pronounced increases in biliary tree pressure than morphine.
Bioavailability:	The degree to which a drug will become available in the system after it is taken orally or injected (parenterally).
Biphasic absorption pattern:	An absorption pattern of a drug that demonstrates two phases, with two distinct and separate serum drug peaks.
Bleeding time:	The amount of time it takes blood to clot.
Circulatory depression:	A reduction in the activity of the heart and normal tone of the blood vessels and can be a side effect of opioids. The clinical findings are low blood pressure and a slow pulse.
Congener:	(also spelled cogener) A substance that is chemically related to another.
Conjugation:	One of the metabolic processes performed by the liver to deactivate drugs in preparation for elimination. A drug changed by this type of metabolism is sometimes referred to as a conjugate.
Controlled-release drug:	The rate at which an oral drug is absorbed depends partly on how quickly it is dissolved in and absorbed from the digestive tract. A drug can be chemically altered (e.g. the pH is altered, causing absorption to be delayed) or placed into a delivery system that alters the rate of release of the drug into the digestive tract in a predictable manner, allowing control over how quickly the drug is absorbed into the system.
Cytochrome P-450 system:	A family of liver enzymes involved in the metabolism of various substances in the body, including drugs. The term is often abbreviated to CYP and then the number of the specific member of the family is given. These enzymes include CYP3A3/4, CYP1A2, and CYP2D6, which are involved in the metabolism of various opioids.
Dealkylation:	To remove a chemical alkyl group from a chemical structure. This is one way the body metabolically alters drugs into inactive forms.
Diversion :	The act of giving one's prescription drugs to others for their use. This may be done in exchange for money.
Drug metabolism:	The process of changing a drug from an active form to a less-active or inert form before it is eliminated from the body. This can occur by means of enzymes in the liver or the kidney.
Elimination half-life:	The amount of time it takes the body to eliminate half of a dose of a drug that has been fully absorbed.

Equianalgesic dose:	The dose of a given drug that is required to reach the same degree of activity as another drug. In the case of opioids, morphine is the standard used to compare potency. Doses of other opioids are often compared to morphine to determine doses that offer equivalent activity.
Excrete:	The process of actively eliminating a molecule from inside a cell into a cavity for the purpose of removing it from the system. For example, a drug molecule may be excreted by a kidney cell into the collecting system of the kidney where it will be transported into the urine.
Formulation:	The form a drug is in for administration. For example, an oral formulation is a form that is meant to be taken orally (by mouth).
Gastric emptying:	The process of the body moving the contents of the stomach into the small intestine.
Genitourinary:	Of or pertaining to the urinary and genital systems.
Hepatic:	By or of the liver.
Hydrophilic:	Literal translation is "water-loving." This refers to the ability of a chemical or agent to easily dissolve into water.
Hypnotic:	Produces drowsiness.
Immediate-release:	A drug (or form of drug) that is absorbed quickly after administration.
Intramuscular:	Into the muscle. This term is used for injections of medications that require administration deep into the muscle tissue.
Kappa receptor:	(also spelled κ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP_2 receptor by the International Union of Pharmacology.
Lipophilic:	Literal translation is "fat-loving." This refers to the ability of a chemical or agent to easily dissolve in lipids, fats, or oils. These agents easily cross cell membranes, because cell membranes are composed of lipids and proteins.
Metastatic tumor:	A tumor that has spread to 1 or more distant sites from the original tumor.
Misuse:	Using a prescribed drug for a reason or in a manner other than that for which it was prescribed.
Mu receptor:	(also spelled μ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP_3 receptor by the International Union of Pharmacology.
Nerve block:	An injection of anesthetic near a major nerve. A steroid may be added to the injection for therapeutic or diagnostic purposes.
Neuropathic :	Generated by the nerves. Neuropathic pain is that which is generated as a result of damage to a nerve.

NMDA receptor:	A subtype of glutamate receptor on neurons. Binding with N-methyl-D-aspartate (NMDA) to these receptors opens calcium channels, allowing signal transmission (e.g. pain signal transmission).
Nociception :	The perception of pain.
Nociceptive:	Relating to the perception of pain. A nociceptive receptor is a pain signal receptor.
Nonopioid analgesic:	A medication that reduces pain through mechanisms other than through stimulating or blocking opioid receptors on nerve cells in the central nervous system. The mechanisms of action of various nonopioid analgesics differ. Barbiturates, such as butalbital, inhibit the gamma-aminobutyric acid neurotransmitter receptors to block signal transmission. Acetaminophen is conjugated with arachidonic acid to form N-arachidonoylphenolamine, a compound known as an endogenous cannabinoid (Bertolini 2006) which is responsible for its analgesic effect. Acetaminophen has also been thought to exert its analgesic effect by inhibiting prostaglandin synthesis in the brain (the prostaglandin inhibition results in a minimal amount of anti-inflammatory effect that is not clinically significant and does not contribute to the analgesic effect). The release of phospholipid from injured cell membranes is converted to arachidonic acid, which in turn is metabolized by a cyclooxygenase or lipoxygenase to produce prostaglandins and other chemicals that mediate inflammation. Non-steroidal anti-inflammatory drugs, such as naproxen sodium, inhibit prostaglandin production, thereby reducing pain signal transmission, and reducing inflammatory responses that contribute to pain.
Opioid:	A drug that is chemically similar to or derived from opium. These drugs act at opioid receptors on nerve cells in the central nervous system to reduce transmission of painful stimuli/impulses.
Opioid Naïve:	This refers to a patient who is not currently or who has not recently been treated with opioids. Opioid-naïve patients have not developed tolerance to the effects of opioids and therefore are started at the low recommended doses.
Opioid receptors:	A receptor is group of cell membrane proteins in nerve cells that cause certain responses in the cell when stimulated or blocked by ligands. Opioid receptors are stimulated or blocked by opioids. There are different classes of opioid receptors, including delta opioid receptors (also known as OP_1 receptors), kappa opioid receptors (also known as OP_2) receptors, and mu opioid receptors (also known as OP_3). Activation of these receptors stimulates specific activities within the activated cell, causing effects such as analgesia, nausea, or somnolence. Blockage of the effects of some types of receptors can cause effects such as anorexia or decreased prolactin release.
Opioid Tolerant:	This refers to a patient who has been taking opioids and has developed physical tolerance to some of the effects of opioids, such as respiratory depression.
Oralet:	Medication in a lozenge form.
Paralytic ileus:	A side effect of opioids that manifests as a functional stoppage of the bowel. The bowel stops all contractions in response to the drug and

	rather than being digested, the contents build up, leading to severe bloating, constipation, and vomiting. In rare cases of severe paralytic ileus with massive dilation of the colon, decompression with colonoscopy and selective use of neostigmine may be necessary. (Saunders 2003, Cowlam 2007) In select patients who cannot be treated with decompression, percutaneous endoscopic colostomy or other invasive procedures may be necessary.
Parenteral:	A non-oral route of administering medicine. This includes intravenous, intramuscular (an injection), rectal suppository, or transcutaneous (through the skin, as with a skin patch).
Partial agonists:	Agents that are only partly effective as agonists. Partial opioid agonists have actions at the opioid receptors that are not as strong as agonists.
pH:	A logarithmic scale used to measure the degree of acidity or alkalinity of a given substance. A lower pH is associated with acidity and a higher pH is associated with alkalinity.
Pharmacodynamics:	Describes the effects of a drug on the body and the relationship between the size of a dose and the degree of these effects. These effects would include therapeutic effects as well as side effects.
Pharmacokinetics:	The collective information about how a drug is absorbed, metabolized by the body, distributed in body tissues, and eliminated from the body.
Plasma terminal half-life:	The amount of time it takes for the drug levels that are already present plus the drug added by a recent dose to fall to half of the peak level. This is applied to drugs for which a steady level is intermittently augmented with additional breakthrough doses.
Platelets:	Independent cell-like bodies in the blood that help form clots. They are actually cell fragments that break off a parent cell (megakaryocyte) and form clots by adhering to damaged tissue.
Polypharmacy:	Taking multiple drugs concurrently. Polypharmacy may be necessary to manage a patient's medical condition(s), however, it increases the potential for side effects and drug interactions.
Potency:	The strength of a drug's effects. This is not to be confused with a higher dose. A very potent drug can have powerful effects at very low doses, whereas a drug with low potency will require large doses to have any effect.
Pro-drug:	A drug that must be metabolized by the liver before it becomes active in the body.
Psychotomimetic effects:	Side effects of drugs that affect mood and thinking.
Pulmonic:	Pertaining to or of the lungs.
Renal:	By or of the kidney.

Rescue (breakthrough) dose:	An additional dose of pain medication above the usual baseline dose for times when pain is worsened (e.g., when a patient with otherwise well-controlled pain overexerts himself or the disease/condition has periodic "flares" of symptoms or breakthrough pain).
Respiratory depression:	A reduction in the amount of respiratory effort that can be a side effect of opioids in the CNS. If this worsens, it can lead to respiratory arrest (the patient ceases to breathe).
Serum half-life:	The amount of time it takes for a drug level in the blood to decrease to one-half of the maximum amount reached. This term is sometimes shortened to "half-life."
Sigma receptors:	Receptors in the central nervous system that appear to be involved in antidepressant effects and antianxiety effects. These receptors also attenuate the pain response in experimental settings, thus these receptors were originally classified as opioid receptors. They are now felt to constitute a distinct class of receptors.
Subcutaneous:	Beneath the skin. This term is used for injections of medications that require administration into the looser tissue under the skin.
Suppository:	A formulation of a drug that can be given rectally.
Titration:	Adjusting the amount to achieve a desired effect.
Vertigo:	Dizziness.

Introduction

Chronic pain is frequently untreated, undertreated, or incorrectly treated. Many patients receive inadequate pain relief because doctors are unwilling to manage chronic pain or do not have sufficient knowledge to treat it properly. Many different therapies are available to treat chronic pain, however. This chapter describes some common strategies of effective pain management and, particularly, the place of opioid medications in these strategies.

Common Pain Therapies

The treatment of chronic benign pain is a diverse topic, because different causes of pain require different therapies. Certain conditions may be almost entirely relieved by a few nerve blocks or injections. Other conditions may require a combination of many different treatments to achieve even a moderate amount of relief. Several basic therapies exist that are frequently used in pain treatment. Most patients are managed through one or a combination of these basic techniques.

Even if we consider a group of patients with the same diagnosis, the treatment of these patients must be individualized. What may be appropriate for a 20 year old may not be appropriate for a patient who is 70. Similarly, a medication that may be quite effective in one person may have unacceptable side effects in another. One individual with severe arthritis may remain cheerful and outgoing, whereas in another person the same disease results in depression that is so severe it becomes more limiting than the arthritis itself.

A basic principle of treating chronic pain is that multimodal therapy, the use of several different types of treatment all focused on relieving the patient's

A basic principle of treating chronic benign pain is that multimodal therapy, that is, the use of several different types of treatment all focused on relieving the patient's symptoms may be required. In small offices and rural settings, the therapies are frequently administered under the guidance of a single healthcare professional. In larger pain clinics, a team of several healthcare providers may each contribute to the patient's care.

Commonly used therapies include:

- nerve blocks
- rehabilitation and physical therapy
- pharmacologic therapy (medications)
- acupuncture
- psychotherapy such as stress management (biofeedback)
- neurosurgical procedures
- and others

In most cases, however, pharmacotherapy provides the mainstay of pain relief. Basic pharmacotherapy usually loosely follows the World Health Organization's guidelines for treating cancer pain, which are discussed in more detail in Chapter 4. In general, these guidelines include using nonopioid analgesics as a foundation of therapy, supplementing them with opioid analgesics as needed, and adding adjunctive medications when appropriate.

General Principles of Pain Management

The basic principles of chronic pain management are as follows:

- The first step in managing pain is a thorough assessment of the patient, including a medical history, a history of the patient's pain, and a physical exam.
- Proper therapy depends on recognizing the source or sources of pain and treating each separately.
- Treatable underlying conditions that are causing or contributing to pain should be managed appropriately.
- If it is not possible to resolve the underlying condition, treatments to relieve the patient's symptoms should be initiated.
- Multimodal therapy (using several different types of therapy) is generally more effective than any single therapy.
- Treatment for each patient must be individualized depending on anatomical pathology, the presence of other diseases, age, social and economic status, emotional state, gender, ethnic background, and other factors.
- The use of nonopioid analgesics and adjuvant agents should be explored.

- Pure opioid agonists, such as morphine, should be used when appropriate. **Mixed agonist-antagonist opioids** may induce a withdrawal syndrome in patients tolerant to opioids.
- Analgesic medications should be prescribed in low doses initially, then titrated upwards as necessary.
- Oral medications should be used whenever possible. Oral opioids are relatively inexpensive and allow the patient to control their own medication.
- When patients have constant, or nearly constant pain, analgesics should be given "ATC" (around the clock), not "PRN" (when necessary). Fixed, regular dosing intervals maintain continuous control of pain. Breakthrough medications are allowed, but frequent episodes of breakthrough pain indicate that the regular "around-the-clock" dosing should be increased.
- There are no "standard" or set doses of opioids. Individuals vary greatly in their metabolism of opioids and different individuals require different doses of the medications.
- Care should be exercised when converting from one analgesic to another, or changing from one route of administration to another, to avoid overdosing or underdosing. Conversion tables are notoriously inaccurate and contradictory.
- Nonpharmacologic therapies should be investigated and used when appropriate.

Review of Key Pharmacologic Agents

Pharmacologic agents provide the mainstay of pain relief for most patients with either chronic benign pain or cancer pain. Pharmacologic agents include both nonopioid analgesics and opioid analgesics. The nonopioid and opioid medications have distinct benefits and drawbacks and these are taken into consideration when choosing a therapy for a patient.

Nonopioid Analgesics

There are 3 general types of nonopioid agents:

- Acetaminophen
- Nonsteroidal anti-inflammatory agents (NSAIDs)
- Aspirin

Acetaminophen (APAP)

Acetaminophen is the most widely used nonopioid analgesic, because it has a low incidence of side effects. Acetaminophen also has a high oral and rectal bioavailability and is available in multiple preparations. The major disadvantage of this drug is that it has no significant anti-inflammatory properties. Toxicity of acetaminophen is limited, but in doses of more than 4 grams per day (two Extra StrengthTylenol® is 1 gram), or 2 grams per day for the elderly. In patients with liver abnormalities (e.g., cirrhosis), liver toxicity is a potential problem. Because acetaminophen is included in many preparations of low-dose opioids (Lortab®, Vicodin®, Percocet®, etc.), patients who take such medications AND additional acetaminophen are at risk of liver toxicity.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The nonsteroidal anti-inflammatory drugs (NSAIDs) are used alone for mild to moderate pain or in combination with opioids for more severe pain. NSAIDs reduce pain largely by suppressing the inflammatory process (although they have some other analgesic effects), so they are most effective when the pain is at least partially caused by inflammation. NSAIDs also inhibit bone nociception (pain generation) by reducing prostaglandin synthesis and are therefore quite effective for the pain caused by metastatic bone cancer.

Individual NSAIDs vary widely in both their ceiling doses and dose-related toxicities. If the NSAID chosen proves ineffective with an adequate trial, another NSAID should be substituted, because individuals often respond differently to different NSAIDs. Like aspirin, the most important side effects of NSAIDs are gastrointestinal: pain, bleeding, ulceration of the stomach and duodenum. The COX-2 specific agents have fewer gastrointestinal effects than do the nonselective agents, but may have a higher incidence of other side effects, particularly on the cardiovascular system. NSAIDs prolong the bleeding time by inhibiting blood platelets, which can contribute to bleeding complications. Additionally, they can have toxic effects on the kidney. The potential toxicity of NSAIDs limits their dose and, to some extent, the duration of therapy. They should only be taken short term.

Aspirin (ASA)

Aspirin is an analgesic, anti-inflammatory, and antipyretic (fever-reducing) drug. Like the NSAIDs, and for the same reasons, aspirin is especially useful for reducing

pain associated with inflammation and metastatic bone disease. However, aspirin, like the NSAIDs, can cause pain, bleeding, and ulceration of the stomach and duodenum (the first part of the small intestine). The risk of these complications increases with prolonged use and the use of higher doses as well as in the elderly. Aspirin also increases bleeding time through its inhibitory actions on blood platelets, which are involved in the formation of blood clots.

Opioid Analgesics

The treatment of moderate to severe pain may require the addition of opioids such as morphine. Opioids relieve pain primarily by binding to opioid receptors throughout the nervous system, activating pain-suppressing pathways.

All opioids stimulate pain-suppressing receptors in the nervous system called "mu" receptors. Partial agonists stimulate the mu receptor but also stimulate a different receptor, called "kappa." Stimulation of the kappa receptor produces analgesic effects as well as unpleasant side effects. Mixed agonist-antagonists both stimulate and suppress responses from receptors on nerve cells. Due to the fact that they are associated with effects other than pure analgesia (stimulation of the mu receptor), partial agonists and mixed agonists-antagonists produce side effects and have a more limited ability to produce analgesia. This limitation is referred to as a ceiling effect. In addition, the antagonist action of the agonist-antagonist agents can potentially block the effects of a pure agonist (like morphine) that a patient may already be taking, potentially precipitating withdrawal symptoms. For these reasons, mixed-agonist-antagonists may have little use in chronic benign pain management.

Three major categories of opioids are available for clinical use:

Agonists

- morphine
  - Sustained released oral forms: KADIAN®, Oramorph®, Avinza®, MS Contin®,
  - Immediate-release oral tablet: MSIR®
  - Short acting (infusion/injection): Astramorph™ PF, Duramorph®, Infumorph®
  - Long-acting Epidural: DepoDur™
  - Suppository: RMS®
  - Liquid (immediate acting): Roxanol™, Roxanol-T™, MSIR® Oral Solution

- fentanyl
  - Oral form: Actiq® Fentora®
  - Transdermal: Duragesic®, Fentanyl Transdermal System, Ionsys™
  - Injection: Sublimaze®, Fentanyl PF Solution
- sufentanil
  - Sufenta® (used as an adjunct to surgical anesthesia and for intubation), Chronogesic™ (in phase III trials for use in chronic pain, not yet FDA approved)
- hydromorphone
  - Oral: Dilaudid® tablets, Dilaudid® liquid
  - Extended-release oral capsules: Palladone™
  - Infusion/Injection/epidural: Dilaudid-HP
- meperidine
  - Oral: Demerol® tablets, Demerol® liquid, Meperitab™, Pethidine
  - Injection/infusion: Demerol®, Mepergan Fortis®
- methadone
  - Oral: Dolophine®, Methadose®, Diskets®
- oxycodone
  - Oral tablets: Percocet®, Tylox®, Roxilox®, Endocet®, OxyIR®, Endocodone®, Percolone®
  - Controlled-release oral tablets: Roxicodone®, OxyContin®,
  - Oral solution: Oxy-Fast®, Roxicodone® Intensol, Eth-OxyDose™
- hydrocodone
  - Oral tablets or liquid: Hycodan®, Mycodone®, Vicodin®, Lortab, Hydromet®, Hydropane®, Tussigon®, Norco
- levorphanol
  - Oral and parenteral: Levo-Dromoran®
- codeine (available in various combinations with acetaminophen, aspirin, cold medication preparations, and promethazine)
  - Oral tablets or solution: Tylenol® with codeine, Capital® with codeine, Tussi-Organindin® NR, Phenergan® with codeine, Fiorinal® with Codeine, Fiorital® with Codeine, Esgic, Fioricet® with Codeine, Phrenilin with Caffeine and Codeine, Phreno-Care™, Ty-PAP with Codeine, Tyalgesic™, Vopac™, Ascomp® with Codeine, Soma® compound with Codeine, Ambenyl®, Bromanyl®, Codeprex™ Pennkinetic® Suspension, Decohistine™ DH, Dihistine® DH, Novahistine® DH, Phenylhistine® DH, Ryna-C®, etc.
- propoxyphene
  - Oral tablets: Darvocet® (propoxyphene compounded with acetaminophen), Darvon® (propoxyphene compounded with aspirin)
- tramadol
  - Oral tablets: Ultram®, Ralivia™ ER, Ralivia™ FlashDose®, Ultram® ER.

- oxymorphone
  - Injection: Numorphan®
  - Oral tablet: Opana®
  - Oral extended-release: Opana® ER
  - Rectal suppository: Numorphan®

Mixed agonist-antagonists

- butorphanol
  - Parenteral: Stadol®
  - Nasal spray: Stadol® NS®
- buprenorphine
  - Parenteral: Buprenex®
  - Sublinqual tablets: Subutex®, Suboxone® (buprenorphine plus naloxone)
- dezocine
  - Parenteral: Dalgan®
- nalbuphine
  - Parenteral: Nubain®
- pentazocine
  - Oral tablet: Talwin®, Talwin®NX (pentazocine plus naloxone)
  - Parenteral: Talwin®

Commonly Prescribed Potent Opioids

Many opioid agonists are used to treat chronic benigh pain. For most opioids, both generic and proprietary preparations are available. Many opioids are available as both immediate-release and controlled-release preparations.

For the last decade, most patients have been prescribed a long-acting or controlled-release "baseline" opioid, with a short-acting "rescue" opioid added for breakthrough pain. In recent years, the use of large amounts of breakthrough medication in chronic benign pain has been questioned, and while still used, it is now administered less frequently.

A number of commonly prescribed opioids are discussed below, because an overview of these medications is appropriate at this time. However, some of the information listed below, such as pharmacokinetics and metabolism, are more completely discussed in Chapter 8. Please plan to review this section again after reading that chapter. Because the emphasis of this manual is on the use of KADIAN®, the controlled-release morphine preparations are discussed together at the end of this section.

Morphine (Immediate Release)

Morphine is considered the "gold standard" for measuring the potency of an opioid for the treatment of pain, because most patients (85% to 95%) respond adequately to regular administration of morphine. Morphine is effective orally and is also available in parenteral and suppository forms. It has no ceiling effect on analgesia and it has known and predictable side effects.

Key abbreviations:

SC – subcutaneous
IM – intramuscular
IV – intravenous
PO – by mouth (per os)
Q – every (Latin "quaque")
mg – milligrams
ml – milliliter
ug–microgram

Table 3-1. Available Morphine Products

Formulation	Product Strengths Available	Dosing Interval
Injection	0.5-25mg/ml	q2 to 6 hr
Liquid	2-20mg/ml	q4 hr
Suppository	5mg, 10mg, 20mg, 30mg	q4 hr
Tablet/Capsule	15mg, 30mg	q4 hr

Dosage

- The usual starting oral dosage is 5-30mg every 4 hours.
- The average maintenance dose is 150 to 200mg daily. Patients with very severe pain may require a higher dose.
- When giving SC or IM injections, 10mg/70 kg body weight provides satisfactory analgesia in most patients with moderate to severe pain.

Pharmacology

- Morphine is a strong opioid agonist.
- The potencies and performances of all other analgesics are measured against morphine.
- Duration of action of morphine is 4 to 5 hours for IM or SC injection, or 4 hours (depending on formulation) for oral administration.
- Morphine is rapidly, but not always predictably, absorbed from the gastrointestinal tract
- After SC, IM, or IV injection, morphine is readily absorbed into the blood.

Pharmacokinetics

- Maximum plasma concentrations of morphine are reached on average 45 minutes after administration of oral morphine sulfate solution.
- It undergoes extensive and variable first-pass metabolism: bioavailability of oral preparations of morphine is only about 15-40%. As a result, morphine has a low oral-to-parenteral potency ratio (1:6 with single doses, improving to 1:2 or 1:3 with repeated dosing), meaning that it is more completely absorbed and is more effective when given parenterally (IV), but that potency improves with repeated oral doses (as the serum levels increase).
- The terminal serum half-life is 2 to 4 hours.
- It is distributed to the skeletal muscle, kidneys, liver, gastrointestinal tract, and brain.
- It is secreted into breast milk and crosses the placenta. Morphine is a Category C drug, as adequate animal studies have not been performed.
- Morphine is conjugated (metabolized) to M3G-and M6G-glucuronides (metabolized forms of morphine) in the liver; M6G has significant analgesic activity.
- About 90% of a dose is excreted through the urine, mainly as conjugates. The remainder is excreted through the bile into the feces.
- Morphine does not accumulate in tissues when given in normal doses.
- The pharmacokinetics are altered in hepatic and renal disease, so that adjustment of doses may occasionally be necessary in hepatically or renally impaired patients
- Obesity may lessen absorption

Side Effect Profile

- Most common side effects in normal doses are constipation (which can generally be managed with appropriate therapy), drowsiness (usually transient), nausea and vomiting (usually transient), dizziness and lightheadedness (usually transient).
- Other side effects include: Respiratory depression, headache, pruritis, etc.
- Cardiovascular alterations: flushing of the face, bradycardia (slow heart rate), tachycardia (fast heart rate), palpitations
- Central nervous system effects: confusion, hallucinations, restlessness, vertigo
- Gastrointestinal tract effects: anorexia, biliary colic
- Genitourinary tract effects: urinary retention, hesitancy
- Inappropriate antidiuretic hormone secretion

- Visual disturbances: blurred vision, diplopia, nystagmus, miosis
- Hypothermia
- Dermatological effects: urticaria and pruritus
- Allergic and anaphylactic reactions
- Withdrawal (abstinence) syndrome
- Major hazards in large doses are respiratory depression, circulatory depression, respiratory arrest, cardiac arrest and/or shock.

Advantages

- Morphine sulphate (MS) is the gold standard analgesic for moderate to severe pain.
- Morphine has no apparent analgesic ceiling effect.
- Easy to administer, allows rapid escalation of dose, widely available and relatively inexpensive. Available in oral, parenteral, and suppository forms.
- Antitussant, antianxiety, and hypnotic properties of morphine can also be very useful in patients with severe cancer pain.

Disadvantages

- Wide variability in metabolism of and response to morphine means doses must be titrated to patient's needs.
- Physical dependence to morphine is inevitable with continuous use. Patients physically dependent on morphine will experience withdrawal (abstinence) syndrome if the drug is withdrawn abruptly.

Potential for abuse.

- More likely to be associated with adverse effects than weak opioids. Adverse events are more likely to occur in opioid naïve patients.
- Acute morphine overdosage can cause life-threatening respiratory depression and other adverse effects, although this occurs rarely, in patients taking morphine for severe pain.

Fentanyl

Fentanyl is a synthetic opioid that was first introduced as an alternative to morphine in 1960. For the next thirty years, it was available only in an injectable form, and was used primarily in anesthetic situations. It is not effective orally because the liver breaks it down too quickly after absorption. In 1990, it was introduced in a transdermal formulation skin patch (Duragesic®) that delivers a steady level of

medication for 72 hours. The fentanyl patch has the advantage of being useful for people who cannot take their medications orally. In 1998, it was introduced as a flavored lozenge on a stick. This form of fentanyl (Actiq®) is placed inside the cheek where it is rapidly absorbed directly into the bloodstream (often within 15 seconds), making it very useful for episodic pain.

Table 3-2. Available Fentanyl Products

Formulation	Products	Dosing Interval
Injection	Sublimaze® or Fentanyl PF solution, 50mcg/ml or Ug	IM/IV/SC injections may be repeated in 30 to 60 minutes. It may also be given as a continuous infusion
Transdermal Patch	Duragesic®, Fentanyl Transdermal System, or Ionsys™ 12mcg/hr, 25mcg/hr, 50mcg/hr, 75mcg/hr, 100mcg/hr	q 48 to 72 hr
Lozenge	Actiq® 200mcg, 400mcg, 600mcg,800mcg, 1200mcg, 1600mcg Fentora® transmucosal 100 mcg	Dose can be repeated 15 minutes after completion of the first dose. Consumption limited to 4 units/day

Therapeutic Use

The injectable form is used for sedation, relief of pain, as a preoperative medication, and an adjunct to general or regional anesthesia. The transdermal product is used in the management of chronic or cancer pain that: 1) cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or PRN dosing with short-acting opioids, and 2) requires continuous opioid administration.

Actiq® is indicated only for the management of breakthrough cancer pain in patients who are tolerant to and currently receiving opioid therapy for persistent cancer pain.

Pharmacology

- Very potent opioid agonist with actions similar to those of morphine. Fentanyl is lipophilic and therefore crosses the blood/brain barrier quickly.
- Approximately 50 to 100 times more potent than morphine; 0.1mg IM is equivalent to morphine 10mg IM.

Duragesic®

Duragesic® (and the generic forms) are dermal patches that contain a reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose. They deliver fentanyl to the skin forming a depot of drug in the upper layers, from which it enters the circulation. An ethylene-vinyl acetate copolymer membrane controls the rate of delivery of fentanyl to the skin surface. Serum fentanyl concentrations are proportional to the dose, thus allowing for accurate individual dose titration. The product is available in 5 strengths (patch sizes); the rate of fentanyl delivery is proportional to the surface area of the patch (See Table 3-3). The Fentanyl Transdermal System by Mylan uses the same mechanism used by Duragesic®. The Ionsys™ transdermal system is composed of a housing that contains a battery and two hydrogel reservoirs with a polyisobutylene skin adhesive. The system is a patient-controlled iontophoretic transdermal system that uses an electrical charge to release a dose from the reservoir.

Table 3-3. Duragesic® Equivalency to PO Morphine

Patch Size	Fentanyl Content	Rate of delivery (µg/hr)
10 cm2	2.5 mg	25µg/hr
20cm2	5.0mg	50µg/hr
30cm2	7.5mg	75µg/hr
40cm2	10mg	100µg/hr
50cm2	12.5mg	125µg/hr

The transdermal patch has a broad range of doses that are equivalent in potency to doses of oral morphine. See Table 3-4 for corresponding morphine doses. In

controlled clinical trials in non-opioid-tolerant patients, 60mg/day IM morphine was considered to provide analgesia approximately equivalent to Duragesic® 100µg/hr. Duragesic® should not be administered to children under 12 years of age or patients under 18 years of age who weigh less than 50kg (110lbs) except in an authorized investigational research setting because it has not been well studied in this patient population. Duragesic® carries the following black box warning regarding use in children: The safety of Duragesic® has not been established in children under 2 years of age. Duragesic® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

Table 3-4 Dose Conversion Guidelines for Duragesic®

Current Morphine Dose	Daily Dosage (mg/dL)			
Oral Morphine	60-134	135-224	225-314	315-404
IM/IV Morphine	10-22	23-37	38-52	53-67
Recommended Duragesic dose	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/hr

Pharmacokinetics

- Injection and lozenge forms have a very quick onset of action. The lozenge is almost as quick as an injection with an onset of action in 5-15 minutes. Peak analgesia is reached within minutes of IV administration.
- The transdermal patch takes much longer to reach analgesic efficacy. Serum fentanyl concentrations increase slowly after application of the fentanyl patch (usually about 12-18 hours), level off after 12 to 24 hours, and remain relatively constant for the remainder of the 72-hour application period. (Peak serum drug levels occur 24 to 72 hours after applying the patch).
- It is rapidly metabolized, primarily by dealkylation to inactive metabolites in the liver and excreted mostly as metabolites in the urine.

Drug Interactions

- Fentanyl is a CYP3A3/4 enzyme substrate. Medications that inhibit these enzymes (eg. erythromycin, ketoconazole, itraconazole, and protease inhibitors) may increase serum concentrations of fentanyl.
- Drugs that increase metabolism through CYP3A3/4, including carbamezapine, phenobarbital, and rifampin, may decrease serum levels of fentanyl by increasing

its metabolism.

- It is unknown whether these interactions are clinically significant, but should be monitored.

Side Effect Profile

- At high doses, can produce marked muscular rigidity. This side effect is typically associated with rapid IV infusion.
- Skin rash around the patch is a common side effect. However, this may often be prevented by pretreating the skin with a steroid spray (e.g. the kind that is used in steroid inhalers for asthma) or skin prep applications.
- Adverse effects can persist for up to 36 hours after removal of the patch because of continued absorption of drug in the skin.

Advantages

- Very potent opioid.
- Less likely than morphine to cause nausea and vomiting when used in equivalent doses.
- Good alternative for those who cannot take oral medications.
- Physicians believe the transdermal patch is less abusable than OxyContin® and MS Contin®.

Disadvantages

- No tablet or capsule formulation of fentanyl is available at this time.
- Analgesic effect cannot be evaluated during the first 18-24 hours due to delay of onset of fentanyl patch.
- With the fentanyl patch, patients often require short-acting analgesics for the first 24 hours.
- There is no opportunity for proper dose titration in the management of acute or postoperative pain, including use in outpatient surgeries.
- Must rotate application site.
- Large dose strength patches are quite wide (2-3 inches across).
- Patients with adverse reactions to fentanyl should be monitored for at least 12 hours after patch removal.
- Patients should be advised to avoid exposing the fentanyl patch application site to direct external heat sources (e.g., heating pads, heat lamps, hot tubs, etc.) while wearing the patch. There is a potential for temperature-dependent increases in fentanyl release from the patch.

- There has been no systematic evaluation of fentanyl as an initial opioid in the treatment of pain.

Hydromorphone

Hydromorphone is a synthetic opioid with somewhat fewer side effects than morphine. Hydromorphone is commonly used as an injectable agent in the hospital and is also available in oral and suppository forms. There is currently no long-acting hydromorphone product on the market, which limits its usefulness in chronic pain (a previously available long-acting form, Palladone™, was removed from the market in 2005). It is a good alternative to morphine, but has a higher abuse potential.

Table 3-5. Available Hydromorphone Products

Formulation	Products and doses available	Dosing Interval
Tablet, immediate-release; Capsule, controlled-release	Dilaudid® 1mg, 2mg, 3mg, 4mg, 8mg	q 4-6 hr; FDA approval pending
Liquid	Dilaudid® 5mg/ml	q 4-6 hr
Suppositories	3mg	q 6-8 hr
Injection	1-4mg/ml IM, SC Dilaudid HP® 10mg/ml	q 4-6 hr

Pharmacology

- Very potent opioid, morphine-derivative
- 1.5mg IM or SC or 7.5mg PO equivalent to morphine 10mg IM or 60mg PO.
- High solubility means large quantities can be given IM in small volumes.
- Duration of action similar to morphine.

Pharmacokinetics

- Similar to morphine.
- Serum terminal half-life is 2 to 3 hours.

Side Effect Profile

- Same as for morphine, but it produces slightly more euphoria.

Advantages

- Alternative to morphine for moderate to severe pain.
- Usually given by injection; large quantities can be given IM in small volumes.

Disadvantages

- Injection can cause local pain and tissue irritation.
- No long-acting product available.
- High abuse potential and high street value.

Meperidine

In its oral form, meperidine is a very short-lived opioid. One of its breakdown products, normeperidine, can cause euphoria, agitation, and decrease the seizure threshold. Prolonged use can cause personality changes and epileptic seizures. For these reasons, meperidine is relatively contraindicated for the treatment of chronic benign pain. This recommendation, however, does not prevent its use in chronic benign pain. It is only available in short-acting formulations either as meperidine alone or in combination with 25mg of promethazine.

Table 3-6. Available Meperidine Products

Formulation	Products	Dosing Interval
Syrup	50mg/5ml)	q 4 hr
Tablet; Liquid	Demerol® 50mg, 100mg	q 4 hr
Tablet with promethazine	Mepergan Fortis® 50mg/25mg Meperitab™ 50mg	q 4-6 hr
Injection with promethazine	Mepergan®25mg/25mg ml	q 4-6 hr

Pharmacology

- Oral meperidine 300mg is equivalent to approximately 30mg of oral morphine.

Pharmacokinetics

- When given orally, 50% of the meperidine dose is metabolized in the first pass through the liver to several metabolites.
- One of the active metabolites, normeperidine, can last in the body for over 15 hours after every dose. Normeperidine levels, therefore, will continuously increase whenever meperidine is used steadily for more than 3 or 4 days. This effect is even greater in persons with renal dysfunction.
- Normeperidine is potentially toxic, causing euphoria, agitation, personality changes, and epileptic seizures. The effects of normeperidine are not reversible by opioid antagonists such as naloxone.
- This metabolite is more likely to accumulate in patients with renal dysfunction, if doses are greater than 600mg per day, and with continuous dosing for longer than 48 hours.

Side Effect Profile

- As with morphine, but may cause more nausea.

Advantages

- None

Disadvantages

- Potential accumulation of toxic metabolite with chronic dosing.
- Not available in a long-acting formulation.

Methadone

Methadone was first synthesized in Germany at the end of World War II and was specifically designed for the treatment of severe chronic cancer pain. In the middle 1960s it became widely used to treat drug addicts because it can suppress drug craving in this population with one daily dose. Because of this, it has developed a reputation as a medication that is linked to addiction. Actually, it is an excellent pain medication. Because of its long duration of action, it may be dosed only 2 or 3 times a day.

Because it has effects on other receptors (NMDA receptors) in addition to opioid receptors, methadone is sometimes effective for treating pain that does not respond to other opioid medications. The major advantage of methadone is its low cost compared with the time-release opioids.

One danger that is specific to methadone is delayed-onset sedation. The other opioids cause their strongest sedating effects within the first day or two of use. Methadone, however, may actually cause more sedation up to 2 weeks after the start of therapy. This makes methadone particularly difficult to titrate or for use in elderly patients.

Table 3-7. Available Methadone Products

Formulation	Products (Manufacturers)	Dosing Interval
Tablets	Dolophin® 5mg, 10mg, 40mg Methadose® 5mg, 10mg Methadose Dispersible Tablet 40mg Diskets® Orodispersable Tablet 50 mg	q 3-8 hr
Oral solution	1-10mg/ml	q 3-8 hr

Therapeutic Uses

- Indicated for the management of severe pain.
- Also used in detoxification and maintenance treatment of narcotic addition. If used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program.
- Strong opioid agonist. Considered by some to be the best alternative for morphine-intolerant patients.
- In single doses, methadone is only marginally more potent than morphine: 10mg IM or 20mg PO equivalent to morphine 10mg IM or 60mg PO.
- In repeated doses, methadone is several times more potent than morphine; oral doses of 20-30mg daily are equianalgesic to 60-90mg or more of morphine PO.
- Duration of action of methadone is 4 to 5 hours after IM injection and 4 to 6 hours after oral administration (i.e., similar to morphine). Duration extends up to 6 to 8 hours after repeated administration.

Pharmacokinetics

- Readily absorbed from the gastrointestinal tract, reaching peak concentrations after about 4 hours.
- Widely distributed in tissues and diffuses across placenta. Extensively metabolized in the liver, mainly by *N*-demethylation. Metabolites excreted in bile and urine.
- Terminal half-life is extremely variable (15 to 40 hours), therefore, accumulation is possible and dosing interval needs to be carefully monitored.

- Accumulation more likely in patients with impaired renal or hepatic function, because both organs are involved with the metabolism of methadone.
- Like morphine, methadone displays wide variability between individuals in concentrations of drug achieved in the blood and rate of elimination of drug from the body. Dosage schedules of methadone must therefore be individualized for each patient.

Drug Interactions

- Methadone is a CYPIA2, 2D6, and 3A3/4 enzyme substrate and a CYP2D6 enzyme inhibitor. CYP3A3/4 and CyP2D6 enzyme inhibitors increase serum methadone concentrations. Enzyme inducers decrease serum methadone concentrations via enhanced hepatic metabolism. Drugs that induce hepatic enzymes and lower methadone serum levels include carbamazapine, St. John's Wort, rifampin, rifapentine, and barbiturates.

Side Effect Profile

- Similar to morphine but with a greater respiratory depressant effect.
- Pulmonary edema after overdosage is a common cause of fatalities among addicts.

Advantages

- Extended duration of action advantageous for patients with chronic benign pain except for tendency of drug to accumulate.
- Tolerance may develop more slowly to methadone than to morphine in some patients.
- Better antitussive and stronger sedative properties than morphine.
- Very effective in suppressing withdrawal symptoms in patients dependent on opioids.

Disadvantages

- Repeated administration may lead to accumulation of the drug (with potential for significant toxicity) because of very long half-life.
- Produces less intense but more prolonged withdrawal symptoms than morphine.
- Use should be restricted to patients intolerant of opioids, and should be used with great caution in elderly patients and patients with hepatic or renal dysfunction, all of whom are more likely to experience accumulation of the drug. Methadone can cause urinary retention and oliguria, which are more likely to occur in patients with bladder obstruction or renal disease. Drug accumulation can develop in patients with hepatic disease due to decreased metabolism. In patients with

hepatic disease, doses may need to be reduced and the patients should be monitored closely for symptoms and signs of toxicity.

- Should also be used with great caution in patients whose compliance or communication with the prescribing physician is in question, such as the confused or demented patients.

Oxycodone

Oxycodone is a synthetic opioid that is roughly 50% more potent than morphine per milligram. Since 1994, it has been available as a long-acting medication (OxyContin®), which is dosed every 8 or 12 hours. The short-acting forms of oxycodone are usually manufactured in combination with acetaminophen (e.g. Percocet®, Tylox®, Roxicet®) or aspirin (e.g. Percodan®).

Therapeutic Use

Oxycodone is used for the management of moderate to severe pain. OxyContin® is indicated for around the clock management of moderate to severe pain when an analgesic agent is needed for an extended period of time.

Table 3-8. Available Oxycodone Products

Formulation	Products	Dosing Interval
Short-acting capsules and tablets with acetaminophen	Percocet® 2.5/325,5/325/7.5/325/10/325/; Tylox® 5/500, Roxilox®, Roxicet®, Endocet®, OxyIR	q 4-6 hr
Short-acting capsule with aspirin	Percodan® 5/500	q 4-6 hr
Capsule, immediate-release	OxyIR® 5mg	q 4-6 hr
Tablet, immediate-release	Roxicodone® 5mg, 15mg, 30mg	q 4-6 hr
Tablet, controlled-release	OxyContin® 10mg, 20mg, 40mg, 80mg	q 8-12 hr
Liquid	Roxicodone® 5mg/ml; Roxicodone Intensol® 20mg/ml Oxyfast Solution 20 mg/mL	q 4-6 hr

Pharmacology

- Oxycodone is a potent opioid agonist derived from morphine and resembling codeine in structure.
- The oral equianalgesic dose of morphine is approximately 1 to 2 times the oral oxycodone dose. For example, 20mg of oral oxycodone is equivalent to 20 to 60mg of morphine.
- Like codeine, oxycodone is about one-half as potent orally as parenterally.

OxyContin®

OxyContin® is a controlled-release product with a biphasic method of action designed to deliver up to a third of its contents in the first hour and then to slowly release the remainder over 8 to 12 hours. Because of this, it has a much quicker onset of action than some controlled-release medications. This may also explain the increase in side effects that sometimes occur when patients are taking higher dosages of this medication.

Pharmacokinetics

- Oxycodone release from OxyContin® is pH independent.
- The absorption of oxycodone is greater than that of morphine.
- Oxycodone is well absorbed from OxyContin® tablets with an oral bioavailability of 60% to 87%. This high oral bioavailability is due to low presystemic and first-pass metabolism.
- In normal volunteers, the absorption half-time (time to half of the total absorption) is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin® exhibits a biphasic absorption pattern with 2 apparent absorption half-lives of 0.6 and 6.9 hours. This describes the initial release of oxycodone from the tablet followed by a prolonged release. However, oxycodone is not released continuously over the dosing interval. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours.
- Dose proportionality or bioavailability has been established for the 10-mg, 20-mg, 40-mg, and 80-mg strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC).
- Approximately 7% of whites, 8% of blacks, and 1% of Asians are poor metabolizers of CYP2D6 and produce no CYP2D6 or undetectable levels of it. Some authorities have reported reduced clinical response to oxycodone in individuals who are CYP2D6 deficient, possibly because of a reduced level of or complete absence of active metabolites (namely oxymorphone and alpha- and

beta-oxymorphol). However, other research suggests that the parent drug, rather than metabolites are responsible for the central effects of oxycodone. (Lalovic 2006, Susce 2006, Tyndale 1997)

- Oxycodone is metabolized to primarily oxymorphone and noroxycodone. Noroxycodone is the major circulating metabolite of oxycodone. Oxymorphone possesses analgesic activity but is present in low plasma concentrations.
- Oxycodone and its metabolites are excreted primarily by the kidney.
- The apparent elimination half-life of oxycodone after the administration of OxyContin® is 4.5 hours compared with 3.2 hours for immediate-release oxycodone.

Drug Interactions

- Medications that interfere with cytochrome P450 2D6 liver enzyme (including some antidepressants such as Prozac® and Paxil®) may reduce the effectiveness of oxycodone. Blockade of this pathway by concomitant medications has not yet been shown to be of clinical significance.

Side Effect Profile

Similar to morphine but with fewer gastrointestinal side effects.

Advantages

- An effective oral alternative to morphine for moderate to severe pain.

Disadvantages

- Deaths from overdose have been reported due to misuse or abuse after crushing or altering the delivery system of OxyContin®.
- OxyContin® serum levels fluctuate because of the early release of 33% of the dose. This peak may be associated with increased side effects.
- Oxycodone used in combination with acetaminophen or aspirin is limited by the maximum dose of the nonopioid product.

Less Commonly Prescribed Potent Opioids

Oxymorphone

Oxymorphone is used for moderate to severe pain. It is available in parenteral, oral, and rectal formulations and offers a potent alternative to morphine.

Table 3-9. Available Oxymorphone Products

Formulation	Products	Dosing Interval
Injection	1 mg/ml, 1.5 mg/ml	q 4-6 hr
Suppository	Numorphan® 5 mg	q 4-6 hr
Oral Tablet	Opana® 5 mg and 10 mg	q 4-6 hr

Pharmacology

- Very potent opioid agonist; 1 mg IM or SC or 6mg rectally equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of oxymorphone is 4 to 6 hours after IM or SC injection (e.g., similar to morphine).
- Duration of action of oral dose is 4 to 6 hours.

Pharmacokinetics

- Similar to morphine.
- Terminal half-life of 2 to 3 hours.
- Steady-state of the oral formulation is reached after 3 days of multiple dose administration.

Side Effect Profile

- Similar to morphine

Advantages

- Potent alternative to morphine injections and suppositories for moderate to severe pain.

Disadvantages

- No antitussive activity.
- Must be taken one hour prior or two hours after eating.

Levorphanol

Levorphanol is occasionally used for moderate to severe pain. It is also used parenterally for preoperative sedation and as an adjuvant to anesthesia.

Table 3-10. Available Levorphanol Products

Formulation	Products (Manufacturers)	Dosing Interval
Injection SC (IV not recommended)	2mg/ml	q 6-8 hr
Tablet	Levo-Dromoran® 2mg (Roche Pharmaceuticals)	q 6-24 hr

Pharmacology

- Very potent opioid agonist: 2-3mg IM or SC or 4mg PO equivalent to morphine 10mg IM or 60mg PO.
- Levorphanol is almost as effective by mouth as by injection.
- Duration of action of levorphanol is 4 to 8 hours after oral administration (i.e., longer than morphine).

Pharmacokinetics

- The metabolism of levorphanol is similar to that of morphine.
- It is rapidly conjugated with glucuronic acid in the liver.
- Plasma levels of the glucuronide conjugate (the metabolized form of the drug) are 5 to 10 times as great as levels of the unconjugated drug.
- The terminal half-life is 12 to 16 hours, which is much longer than that of morphine. This long half-life may lead to accumulation of the drug in tissues in a manner similar to that for methadone.

Side Effect Profile

- Same as for morphine, but less likely to cause nausea, vomiting, and constipation than morphine and has greater sedative effects.
- Levorphanol accumulates in the tissue in a mechanism similar to methadone.
- Frequent monitoring is required to minimize side effects.

Advantages

- Effective orally.
- More potent and has longer duration of action than morphine.
- Greater sedative effect than morphine (sometimes could be advantageous).
- Antitussive

Disadvantages

- Like methadone, repeated administration leads to accumulation of the drug with potential for significant toxicity-because of very long half-life.
- Greater sedative effect than morphine.
- Same precautions should be used with this drug as with methadone.

Less Potent Opioids

Hydrocodone

Hydrocodone is very commonly used to treat mild to moderate pain. It is typically given to chronic pain patients for breakthrough or incident rescue pain. It is available in several different strengths, all combined with acetaminophen, aspirin, or ibuprofen (Lortab®, Vicodin®, Vicoprofen®, Norco, etc.) and is generally effective for 3 to 4 hours. It is also available in antitussive syrup (Tussionex®) which is dosed every 12 hours.

In addition to its use in mild to moderate pain, hydrocodone is also frequently used as a rescue medication in patients with chronic benign pain. All hydrocodone analgesic formulations have a ceiling effect due to the nonopioid content. Acetaminophen and aspirin dosing should not exceed 4 grams per day. Ibuprofen is limited to 3200mg/day for otherwise healthy individuals. Less than 4 grams per day (2 grams for the elderly) of acetaminophen or aspirin may be the limit for the elderly population

Codeine

Codeine is probably the most commonly prescribed opioid in the world. Because it is a fairly weak medication that lasts for only 3 or 4 hours, it is most appropriate for mild pain. It is associated with a greater incidence of side effects (especially nausea, hives, itching) than some other opioids. It is primarily available in combination with acetaminophen and aspirin. It may be used to treat mild pain from conditions such as mild injuries or mild dental pain. It is also used as in combination with expectorants and/or decongestants as an anti-tussive.

Propoxyphene

Propoxyphene (Darvon®, Darvocet®) is a very weak opioid medication that in some studies has not been shown to be any more effective than acetaminophen. At the

same time, some patients can get 3 to 6 hours of relief from mild to moderate pain with this medication. Propoxyphene is also only available in combination with nonopioid products.

Tramadol

Tramadol is a synthetic pain reliever with weak opioid effects. It also inhibits the reuptake of norepinephrine and serotonin. It is not a controlled substance although some states have imposed regulations on the medication. It is generally considered to be less potent than codeine, which is one of the weaker opioids. Nevertheless, tramadol has proven to be useful for some people with mild to moderate pain levels. Tramadol is dosed every 4 to 6 hours and must not exceed 400 mg/day. Doses above this limit are associated with an increased risk of seizure. Tramadol causes less constipation and sedation than the other opioids but can cause considerable nausea.

U.S. Drug Enforcement Administration Schedule of Controlled Substances	
Schedule I	A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.
Schedule II	(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. (C) Abuse of the drug or other substances may lead to severe psychological or physical

	dependence.

U.S. Drug Enforcement Administration Schedule of Controlled Substances *continued*	
Schedule III	(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
Schedule IV	(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.
Schedule V	A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

Mixed Agonist-Antagonist Opioids

Traditional opioids stimulate the mu receptor. Mixed agonist-antagonists stimulate the kappa receptor and at least partially block the mu receptor. They were originally believed to cause less respiratory depression. However, at therapeutic doses, the risk of respiratory depression is equivalent to that of traditional opioids. The agonist-antagonists do have a ceiling effect to respiratory depression, just as they have a ceiling effect for analgesia. Basically, this means at very high doses the risk of respiratory depression does not increase any further.

Mixed opioid agonist-antagonists are usually not recommended for use in chronic benign pain. In addition, if a chronic pain patient who has been on mu agonists is given a mixed agonist-antagonist, opioid withdrawal may result. This occurs because the mixed opioid may block the mu receptor which was previously stimulated by the mu agonist.

Butorphanol

Butorphanol is used in the management of moderate to severe pain including migraine headache.

Table 3-11. Available Butorphanol Products

Formulation	Products	Dosing Interval
Injection	Stadol® 1-2mg/ml	q 6 hrs
Nasal Spray	Stadol® 1mg/inhalation	Initial may be followed by a second dose in 90—120 minutes. This sequence can be repeated every 3 to 4 hours

Pharmacology

- Mixed agonist-antagonist morphine congener with profile of actions similar to pentazocine.
- Far more potent than morphine; 2-3mg IM equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of butorphanol is 3 to 4 hours after intramuscular administration (slightly less than morphine).

Pharmacokinetics

- Absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism.

- Extensively metabolized through hydroxylation and *N*-dealkylation; less than 5% excreted unchanged.
- Butorphanol and metabolites are excreted mainly in the urine.
- Plasma half-life is 2.5 to 3.5 hours.

Side Effect Profile

- Same as for morphine, although less likely to produce respiratory depression at high doses.
- Can produce prominent psychotomimetic effects (e.g., confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis), although to a lesser degree than pentazocine.
- May also increase pulmonary and aortic blood pressure as well as increase cardiac work.

Advantages

- Potent analgesic agent, less likely than morphine to produce respiratory depression.

Disadvantages

- As a mixed agonist-antagonist at opioid receptors, butorphanol is not recommended for continuous treatment of chronic cancer pain.
- Ceiling analgesic effect and an associated increased risk of psychotomimetic side effects
- Potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.
- Can also have serious adverse hemodynamic effects, such as increased pulmonary artery pressure and systemic blood pressure.
- No oral formulation available.

Pentazocine

Used to treat moderate to severe chronic pain; better suited for relief of acute rather than chronic pain.

Table 3-12. Available Pertazocine Products

Formulation	Products	Dosing Interval
Injection	30mg/ml	q 3-4 hr
Tablet	Talwin® 50mg	q 3-4 hr
Tablet with acetaminophen	Talacen® 25mg/650mg	q 3-4 hr
Tablet with aspirin	Talwin Compound® 12.5mg/325mg	q 3-4 hr
Tablet with aspirin and caffeine	Talwin Compound 50® 50mg/390mg/32mg	q 3-4 hr
Tablet with naloxone	Talwin NX® 50mg/0.5 mg (	q 3-4 hr

Pharmacology

- Strong mixed agonist-antagonist opioid.
- Far less potent than morphine; 30-60mg IM or SC or 150-180mg PO equivalent to morphine 10mg IM or 60mg PO.
- Oral 50mg dose results in analgesia equivalent to that produced by 60mg codeine.
- Duration of action of pentazocine is 2 to 3 hours after intramuscular administration (e.g., less than morphine).

Pharmacokinetics

- May be erratically absorbed from the gastrointestinal tract and undergoes significant first-pass metabolism after oral administration.
- Metabolized chiefly in the liver and excreted mainly as metabolites in the urine.
- Plasma half-life is 2 to 4 hours.
- Displays wide variability among individuals in the concentrations of drug achieved in the blood and rate of elimination of drug from the body after parenteral administration. Appropriate dosing schedules must therefore be individualized for each patient.

Side Effect Profile

- Similar to morphine, although less likely to produce vomiting or respiratory depression.
- Its use may be associated with marked delays in gastric emptying and thus the potential to alter absorption of other orally administered drugs. Also associated with rapid development of tolerance. Of all the mixed agonist-antagonist opioids, pentazocine has the greatest potential to produce prominent psychotomimetic

effects (e.g., confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis).

- May also increase pulmonary and aortic blood pressure as well as increase cardiac work. Abrupt discontinuation of drug after prolonged use causes severe withdrawal syndrome, often worse than that caused by morphine or other opioids.
- Injections may be painful; local tissue damage, including fibrosis (subcutaneous tissue scarring), may occur at injection sites, particularly after SC injection or multiple doses.

Advantages

- Effective orally.
- Less likely than morphine to produce respiratory depression and physical dependence.

Disadvantages

- Pentazocine is not recommended for continuous treatment of chronic cancer pain because of a ceiling analgesic effect, associated increased risk of psychotomimetic side effects, and a potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.
- May be absorbed erratically.
- Can have serious adverse hemodynamic effects. Hypotension, hypertension, and tachycardia have been reported.
- May be associated with pain and tissue damage with repeated injections.
- Rapidly induces tolerance and may cause very severe withdrawal syndrome when administration is terminated abruptly.

Nalbuphine

Nalbuphine is used in the relief of moderately severe pain. It is also used for preoperative analgesia and in anesthesia.

Table 3-13. Available Nalbuphine Products

Formulation	Products	Dosing Interval
Injection	Nubain® 1.5-20mg/ml	q 3-6 hr

Pharmacology

- Analgesic potency similar to morphine; 10mg IM equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of nalbuphine is 4 to 6 hours after intramuscular administration (e.g., similar to morphine).

Pharmacokinetics

- After IM administration nalbuphine is metabolized chiefly in the liver and excreted predominantly in the feces.
- Considerable first-pass metabolism after administration by mouth.
- Plasma half-life 2 to 5 hours.

Side Effect Profile

- Similar to morphine, although less likely to produce respiratory depression and physical dependence.
- Substantial potential (although less than pentazocine) to cause psychotomimetic effects (e.g. confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis).

Advantages

- Opioid analgesic with similar potency and duration of analgesic action to morphine.
- Less likely to produce respiratory depression and physical dependence than morphine.
- Less potential to cause psychotomimetic and hemodynamic adverse effects than pentazocine.

Disadvantages

- As a mixed agonist-antagonist at opioid receptors, nalbuphine is not recommended for continuous treatment of chronic cancer pain because of its ceiling analgesic effect, associated increased risk of psychotomimetic side effects, and potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.

- No oral formulation is available.

Controlled-Release Morphine Compounds

Conventional, immediate-release formulations of opioids have been available for many years. The challenge in improving chronic pain management has not been in the development of new drugs with new actions or better potency, but rather improvements in the way in which the drug is delivered. This section provides information concerning KADIAN® and other sustained-release or controlled-release formulations of morphine. Specifically, the differences between the products are addressed.

KADIAN®
(Actavis Pharmaceuticals, LLC)
Modified-Release Composition

KADIAN® capsules contain polymer-coated, extended-release pellets of morphine sulfate. The gelatin capsule dissolves quickly in the stomach, freeing the polymer-coated pellets. As the pellets pass into the less acidic small intestine, morphine release is greatly accelerated. The pellets develop minute holes through which the morphine diffuses. The pellets are formulated so that morphine is released over several hours, resulting in plasma morphine concentrations which are maintained for up to a 24-hour period.

Product Strengths

- Color-coded gelatin capsules in 8 strengths: 10mg (light blue);20mg (yellow), 30mg (blue violet), 50mg (blue), 60mg (pink), 80 mg(light orange) 100mg (green) and 200mg(light brown).*Pharmacokinetics*
- Up to 24-hour release profile.
- Minimally affected by presence of food.
- Absorption: extent comparable, but rate slower than all other oral morphine formulations.
- The minimum peak serum concentration (C_{min}) for KADIAN® is higher than for MS Contin®, thus producing less fluctuation in plasma levels.
- The time to maximum plasma levels (*T*max) is 8.6 hours.

Indications

- Prolonged relief of moderate to severe chronic pain where treatment with an opioid analgesic is indicated for more than a few days.

Contraindications

- Hypersensitivity to morphine, morphine salts or any of the capsule components. True hypersensitivity is rare, most untoward effects are side effects of the medication.
- Patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings)
- Patients with acute or severe bronchial asthma or hypercardia.
- Patients who have or are suspected of having paralytic ileus.

Precautions

- As for morphine, plus only for chronic use (more than several days) and should be withdrawn within 24 hours of cordotomy or similar surgery.

Dosage and Administration

- Administer q12h to q24h.
- Patients who do not have a proven tolerance to opioids should be started only on the 20mg strength.
- Dosage titration should generally be increased by 48 hour increments.
- Breakthrough pain may require supplementation with short-acting (immediate-release) morphine.
- Morphine supplementation allows treatment with the same compound for both chronic pain management and breakthrough pain.
- In general, capsules (and pellets) should be swallowed whole and should not be chewed, crushed, or dissolved.
- As an alternative to ingesting whole capsules, the capsule may be opened and the pellets can be ingested with a small amount of applesauce (sprinkle administration) or the pellets may be mixed with a small amount of water and administered through a 16 French or larger gastrostomy tube (a tube going into the stomach for the purpose of feeding a patient; also known as a G-tube).
- The administration of KADIAN® pellets through a nasogastric tube (a tube that goes through the nose, down the esophagus and into the stomach) should not be attempted.

MS Contin®

Modified-Release Composition

MS Contin® tablets are film-coated and contain wax-coated controlled-release granules of hydroxyalkyline cellulose to which morphine sulfate is adsorbed. Gastric juices dissolve the tablet surface and expose the wax-coated granules. The wax coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream. Thus morphine release is controlled as a result of the extra time it takes the tablet to disintegrate, the wax to dissolve, and the morphine to diffuse from the cellulose.

Product Strengths

- Sustained-release tablets in 5 strengths: 15mg, 30mg, 60mg, 100mg, 200mg. (Note: 200mg tablets are for use in opioid-tolerant patients only.)
- Generic products are also available.

Pharmacokinetics

- Unaffected by food.
- Does not release morphine continuously over the dosing interval.
- Absorption: extent comparable but rate slower than oral immediate-release morphine sulfate.
- Time to maximum plasma levels is 2.5 hours.

Indications

- For management of moderate to severe chronic pain when a continuous, around-the-clock, opioid analgesic is needed for an extended period of time.

Contraindications

- Same contraindications as for morphine.
- Paralytic ileus.

Precautions

- Same precautions as for morphine.
- Only for chronic use (more than several days).
- Should be withdrawn within 24 hours of cordotomy or similar surgery .This is because severe pain antagonizes the subjective and respiratory depressant actions of morphine and abrupt removal of the pain may allow these actions to become manifest.

Dosage and Administration

- Approved for 12-hour administration; but clinical experience suggests that 8 hour

administration is necessary for some patients.

- There has been no systematic evaluation of MS Contin® as an initial opioid in the treatment of pain.
- Breakthrough pain may require supplementation with short-acting (immediate-release) morphine or shortening of the dosing-interval of MS Contin® from 12-hour to 8-hour.
- Tablets should be swallowed whole and should not be broken, chewed, or crushed.
- 200mg tablets are for use in opioid-tolerant patients only.

Oramorph® SR

Modified-Release Composition

Oramorph® SR tablets contain sustained-release granules of hydroxypropyl methylcellulose to which morphine sulfate is adsorbed.

Product Strengths

White tablet embossed in 4 strengths: 15mg, 30mg, 60mg, 100mg.

Pharmacokinetics

- Pharmacokinetics of Oramorph® SR shows considerable intersubject variation.
- Pharmacokinetics unaffected by food.
- Oramorph® SR does not release morphine continuously over the course of the dosing interval.
- Absorption: extent comparable but rate slower than oral immediate-release morphine sulfate.
- Less fluctuation between single dose peak plasma morphine concentrations compared with immediate-release morphine or MS Contin®.

Indications

- Relief of pain in patients who require opioid analgesics for more than a few days.

Contraindications

- As for morphine, plus paralytic ileus.

Precautions

- As for morphine, plus only for chronic use (more than several days).

Dosage and Administration

- Considerations as for morphine plus:
  - Administer 12-hourly.
  - The dosing interval should not be extended beyond 12 hours or shortened to less than 8 hours.
  - The 30mg tablet strength is recommended for the initial titration period.
  - There has been no systematic evaluation of Oramorph® SR as an initial opioid for the treatment of pain.
  - Tablets should be swallowed whole and should not be broken, chewed, or crushed.

Avinza®

Modified-Release Composition

Avinza® Capsules contain polymer-coated, sustained-release pellets of morphine sulfate. The capsules use the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology to produce an extended-release component of Avinza®. The preparation consists of 2 components, an immediate-release component that rapidly achieves plateau morphine concentrations and an extended-release component that maintains plasma concentrations throughout the 24-hour dosing interval.

As the capsule passes through the GI tract, soluble polymers of ammonio methacrylate dissolve leaving pores within the outer membrane. Fluid enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the dissolution phase. This is mediated by fumaric acid, which acts as an osmotic agent and a local pH modifier. Doses above 1600mg per day contain a quantity of fumaric acid which has not been demonstrated to be safe and which may result in serious renal toxicity.

Product Strengths

- Capsules available in 4 strengths: 30, 60, 90, or 120mg.

Pharmacokinetics

- Up to 24-hour release profile.
- Minimally affected by presence of food.
- The extent of absorption is comparable with other extended-release morphine formulations.

- Plasma *T*max is approximately 0.5 to 1 hour.

Indications

- Intended for once daily administration.
- Indicated for the relief of moderate to severe pain requiring continuous, around the clock opioid therapy for an extended period of time.
- Not intended for use as a PRN analgesic.

Contraindications

- Known or hypersensitivity to morphine, morphine salts or any components of the product
- In patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma
- In patients who have or are suspected of having paralytic ileus.

Precautions

- Same as for morphine.
- Only for chronic use (more than several days).

Dosage and Administration

- Avinza® should not be given more frequently than every 24 hours.
- The 30mg capsule strength is recommended for the initial titration period.
- There has been no systematic evaluation of Avinza® as an initial opioid in the treatment of pain.
- Capsules should be swallowed whole and should not be broken, chewed, sprinkled on food, or crushed.

Adjuvant Drugs

Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. In some cases, such as the use of antidepressants, the adjuvant medications are used "as indicated" to treat a symptom associated with pain. In other cases, such as the use of antiseizure medications to treat neuropathic pain, the mechanisms of benefit are not clearly understood. The most commonly prescribed adjuvants are antidepressants (for depression or neuropathic pain), anticonvulsants (particularly for neuropathic pain), benzodiazepines (for anxiety, muscle spasm, and muscle pain), and corticosteroids (for metastatic cancer pain and some types of inflammation).

Tricyclic Antidepressants

Antidepressant medications have been used as analgesics for chronic pain for over 25 years. The older, tricyclic antidepressants (TCA), such as amitriptyline, appear to work better for this purpose than the newer antidepressant medications (SSRIs). TCAs can stimulate the body's natural pain-relieving pathways and thus potentiate the analgesic effects of opioid medications. (Dick 2007) The analgesic effects of amitriptyline and morphine are synergistic. The sedation caused by the tricyclics may be used to help chronic pain patients sleep. (Luccarini 2004) Currently, more than half of the prescriptions for tricyclic antidepressant medications are given for pain rather than for depression.

The peak effects of tricyclic antidepressants are not reached until several weeks after starting on the medication. The dosage needed to relieve pain is generally less than the dosage required to treat depression. Amitryptaline (Elavil®) is the most commonly used TCA adjuvant. Nortriptyline (Pamelor®), imipramine (Tofranil®) and doxepin (Sinequan®) are alternatives. Desipramine (Norpramine®) has been found to be especially useful in neuropathic pain and may have less sedative effects than the other tricyclics. The side effects of the TCAs include morning sedation, a drop in blood pressure on standing (postural hypotension), weight gain, and dry mouth.

Other Antidepressants

The newer class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have largely replaced the tricyclic medications for the treatment of depression because they work more rapidly and have fewer side effects. Identifiable depression occurs in up to 25% of chronic pain patients; therefore, these agents are frequently prescribed. Unlike the tricyclics, the SSRIs have not been clearly demonstrated to have any pain-relieving effects. It should be noted that some SSRI's might reduce the effectiveness of certain opioids, such as oxycodone and hydrocodone, which must be activated in the liver before they become effective.

Anticonvulsants

Anticonvulsants are medications used to control neurological conditions such as epilepsy (seizures). They are also frequently used to treat neuropathic pain conditions. Gabapentin (Neurontin®) is the anticonvulsant used most frequently for this purpose. Patients with neuropathic pain sometimes find the relief they get from

gabapentin is better than the relief they get from opioids. It also improves the quality of sleep and in some people has mild mood-elevating effects. Gabapentin is not metabolized; it is excreted by the kidneys in its unchanged form. Because of this, it has no interactions with other medications and can be safely used even by persons with severe liver disease.

Pregabalin (Lyrica®) is structurally similar to gabapentin and has antiepileptic, analgesic, and anti-anxiety properties. It is indicated for the treatment of neuropathic pain associated with peripheral diabetic neuropathy, postherpetic neuralgia, and for treatment of moderate somatic pain (such as post-operative dental pain). It is taken orally, reaching a peak plasma concentration within 1.5 hours of ingestion. Pregabalin undergoes minimal metabolism. The primary route of excretion is renal. Dose adjustments are needed in patients with renal impairment.

Carbemazepine (Tegretol®, Epitrol®), phenytoin (Dilantin®), phenobarbital (Primidone®), and valproate (Depakote®) are also used to treat neuropathic pain. Lamotrigine (Lamictal®) is a new anticonvulsant that has been effective in the treatment of stubborn neuropathic pain, at least in a few cases. However, it has been associated with severe and even dangerous skin rashes if the dose is escalated too quickly, so many doctors prefer to limit its use.

Benzodiazepines

The benzodiazepine class of medications includes the minor tranquilizers such as diazepam (Valium®), lorazepam (Ativan®), alprazolam (Xanax®), and oxazepam (Serax®), as well as many of the commonly used sleeping pills. All of these medications work at GABA-A receptors in the brain. There is considerable controversy over the use of benzodiazepine medications for the treatment of chronic benign pain. Some physicians feel that benzodiazepines are inappropriate because they are habit forming. However, they can be helpful in treating anxiety and insomnia that sometimes accompany chronic benign pain. They may also be used to treat muscle spasms and certain types of pain originating in muscles.

Corticosteroids

Corticosteroids are more potent inhibitors of inflammation than the NSAID medications and may have an additional analgesic effect. They are frequently used to treat cancer pain arising from bony metastases or tumor infiltration and are sometimes

used to treat acute episodes of benign pain. However, they have significant side effects if used for a prolonged period.

Stimulants

Stimulants such as amphetamine (Dexedrine®) and methylphenidate (Ritalin®) have found limited use as adjuvants. Their primary indication in chronic pain is to counteract sedation in cancer patients who require very high-dose opioids. The side effects of stimulants include anxiety, tremulousness, loss of appetite and, rarely, psychological effects including delirium (severe mental disturbance, sometimes including hallucinations) or paranoia.

Dose Titration

Dose titration to effect is an important principle in both opioid and adjuvant medication therapy. For most of these medications, the dose should be gradually increased until pain relief is satisfactory or intolerable side effects occur. The lowest dose that produces analgesia is best, because this is less likely to produce side effects. Usually, the dose, rather than the frequency of dosage, is increased when titrating, with increases made every 2 to 3 days. .

Titration of drugs (sustained release increases) should be carried out as quickly as possible, (2-3 days), to prevent the patient from experiencing pain or side effects for longer than necessary. However, the time course of action of the medication must be considered when doing so. An adjunctive medication that is expected to take days to develop an effect (such as anticonvulsants) may only be titrated upward every week or two.

Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is

Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to these medications. In practice, however, although this is sometimes performed in cases of cancer pain, most physicians will try an alternative medication once they have exceeded their own comfort level with a given drug. When the opioid is combined with another medication (such as Lortab® or Percocet®) or if the delivery vehicle contains potentially toxic agents (such as Avinza®) the ability to titrate upward may be limited. Additionally, side effects, and costs of medications, become issues when very high doses of opioids are required.

Tapering doses

Morphine therapy should be withdrawn slowly in patients on doses higher than 30mg/day to prevent signs and symptoms of opiate withdrawal. The daily dose should be reduced by 50% for the first two days and then by 25% every two days thereafter until the total dose is equal to the initial dose recommended for opiate-naïve patients (15 to 30 mg/day). Once the 15 to 30 mg/day range is reached, therapy can be discontinued.

Nonpharmacologic Treatment of Pain

Although medication alone can effectively control chronic pain in many patients, several other strategies can and should be used in more difficult cases. Nonpharmacologic strategies are commonly used in patients with chronic benign pain and are indicated in cancer patients who continue to have pain despite optimal medical management.

Neural Blockade (Regional Analgesia)

Peripheral transmission of pain can be interrupted temporarily by the injection of local anesthetic agents near nerves, providing immediate relief of uncontrolled pain. In some cases, anesthetic blocks may provide partial or complete pain relief for prolonged periods, although the mechanism by which this occurs is not clear. Anesthetic nerve blocks can be performed at nerve endings in painful tissues, at various target points along the course of peripheral nerves, or at nerve roots near their attachment to the spinal cord.

Nerve blocks are most commonly used for problems involving the spine or when peripheral nerves are irritated or compressed. They can be used for diagnostic or therapeutic purposes. They are also used to treat painful conditions involving the sympathetic nervous system and can be used for diagnostic and therapeutic purposes. Nerve blocks using neurodestructive chemicals, such as phenol, are sometimes used to destroy nerves carrying pain messages in rare cases of terminal cancer pain.

Physical Therapy

Physical therapy is most commonly used to help restore physical strength and functioning after injury or surgery. Physical therapists can also provide pain relief for patients with musculoskeletal (involving the bones and muscles) pain, some types of neuropathic pain, and sympathetically mediated pain through stretching, movement,

water therapy, heat and cold therapy, etc. Many pain centers have their own physical therapy programs designed specifically to treat persons with chronic pain.

Acupuncture

Acupuncture has been practiced in China for over 5000 years. It has been claimed to treat many conditions, including several causes of pain. Much of the evidence in support of acupuncture is anecdotal (based on individual patient's reports of benefit, rather than from controlled studies). However, some studies have shown benefit. In a small, recent study, acupuncture at the most painful point was shown to relieve back pain. In other studies, a combination of acupuncture with massage offered additional relief over standard pain management alone and acupuncture appeared to be beneficial in treatment of migraine. Another study demonstrated effectiveness for patients with pain due to osteoarthritis. An additional benefit of acupuncture is the relative safety and lack of side effects. (Mehling 2007, Michalek-Sauberer 2007, Linde 2007, Weidenhammer 2007, Eisenberg 2007, Inoue 2006, Witt 2006)

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS stands for transcutaneous (meaning across the skin) electrical nerve stimulation. A TENS device applies a controlled, low-voltage electrical current through electrodes placed on the skin. Theoretically, the current will interfere with the ability of nerves to transmit pain signals to the spinal cord and brain. However, even after several decades of research, it still is not clear whether TENS provides any better pain relief than placebo.

Biofeedback

Biofeedback uses monitoring electrodes placed on the body or scalp and connected to amplifiers. During biofeedback sessions, a therapist helps the patient learn how to mentally control and change the signals from the electrodes, gaining conscious control over normally unconscious functions. Biofeedback is most commonly used to relax spasmed muscles and reduce stress. It has the advantages of being noninvasive, inexpensive, and safe, but usually requires between 5 and 15 sessions before effective control is achieved.

Drug Infusion Pumps

Drug infusion devices (also called implanted infusion pumps) have been available since the 1980s. An electrical or mechanical pump containing a drug reservoir is totally implanted under the skin, infusing the drug through a small catheter directly

into the patient's intraspinal space 24 hours a day. The medication reservoir is filled at the healthcare professional's office every few weeks, and the rate of infusion can be changed as conditions require. Very small quantities of drug are given in the spinal fluid (ug vs. mg). This provides the same relief as larger doses given by mouth or intravenously; so patients have potentially fewer side effects.

Intraspinal infusion devices have their own set of concerns, including device malfunction, catheter obstructions, and the possibility of developing infections. Most pumps run on an internal battery that must be changed (requiring a surgical procedure) every 7-10 years. They are also not effective in every case, so a trial of intraspinal medication must be given before deciding if an infusion pump is indicated. In a small study of patients receiving intraspinal morphine (12 patients) with an implanted pump, patients overall reported a 42% reduction in pain. In a study of the use of polyanalgesia (morphine mixed with additional pain medications), 19 out of 26 patients reported excellent or good long term efficacy. (Valentino 1998, Rainov 2001)

Neurostimulation

Neurostimulation involves implanting a computerized generator and electrodes near the spinal cord, peripheral nerves, or within the brain. Neurostimulators have been used successfully for a variety of pain syndromes. These devices are effective in treating neuropathic pain and pain associated with central neurologic diseases. Implantation of spinal cord stimulators has been shown to relieve refractory angina pectoris pain, intractable headaches, and even chronic pelvic pain. The vast majority of neurostimulators are placed in the epidural space near the spinal cord. Complications from spinal cord stimulation are less common than with implanted infusion pumps, but are still significant. Infections, migration of a lead, spinal fluid leaks, and spinal cord injuries may all occur. Stimulation can only be used for pain involving an isolated area of the body, such as a leg or hand. For this reason, the technique is not useful in cancer patients whose pain may spread as the tumor grows. (Ansari 2007, Weiner 2007, Birknes 2006, Kapural 2006)

Summary

Treatments that resolve the painful condition should be explored whenever possible. If it is not possible to resolve the condition, treatments to relieve the patient's symptoms should be explored.

Multimodal therapy (using several different types of therapy) is generally more effective than any single therapy. The use of nonopioid analgesics and adjuvant agents should always be explored first.

Pharmacologic treatment is the primary therapy for most pain patients, especially cancer patients.

Pure opioid agonists, such as morphine, should be used in most cases. Mixed agonist-antagonist opioids may induce a withdrawal syndrome in patients tolerant to opioids. Analgesic drugs may need to be prescribed in low doses initially for opioid-naïve patients and then be titrated upward as necessary. Patients with severe pain may require higher initial dosing.

Oral medications should be used whenever possible. Oral opioids are relatively inexpensive and allow the patient control of their own medication.

Nonpharmacologic interventions for pain include neural blockade, physical therapy, acupuncture, TENS, biofeedback, infusion pumps, and neurostimualation.

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Self-Assessment Test

Circle the best response

1). Which of the following are used as adjuncts to opioid medication in the treatment of chronic pain?
   a. Nerve blocks
   b. Physical therapy
   c. Counseling
   d. All of the above

2). Which statement concerning the management of a chronic benign pain patient is FALSE?
   a. The first step in managing pain is to prescribe pain medication.
   b. Proper therapy depends on recognizing the source or sources of pain.
   c. Multimodal therapy is generally more effective than any single therapy.
   d. Treatment for each patient must be individualized.

3). When using opioids to treat chronic benign pain, agonist-antagonist or partial agonist medications should not be used because they might:
   a. Cause withdrawal syndrome in patients on chronic pain therapy with agonist agents
   b. Result in seizures
   c. Counteract the effect of nerve blocks
   d. Increase depression

4). Patients with constant pain should receive opiates:
   a. At fixed doses, around the clock
   b. Whenever they need them
   c. About every two weeks
   d. With meals

5). Which of the following types of medication have a ceiling effect, i.e., a dose level above which additional increases produce no further analgesic effect?
   a. Opioid agonist/antagonist or partial agonist analgesics
   b. Antiseizure medications
   c. Tranquilizers
   d. Nonopioid analgesics

6). Which medications largely reduce pain by suppressing the inflammatory process?
   a. Opioids
   b. Tricyclics
   c. NSAIDs
   d. Acetaminophen

7). How long does it take Duragesic® to approximately achieve a steady blood level?
   a. 4 hours
   b. 8 hours
   c. 12 hours
   d. 24 hours

8). What portion of a dose of OxyContin® is delivered within the first hour after taking the drug?
   a. One tenth
   b. One third
   c. One half
   d. Two thirds

9). What types of antidepressant drugs have pain-relieving effects?
   a. Selective Serotonin Reuptake Inhibitors (SSRIs)
   b. Monoamine Oxidase Inhibitors (MAOs)
   c. Tricyclic Antidepressants (TCAs)
   d. Benzodiazepines (BZDs)

10). The class of medications commonly used to treat neuropathic pain is:
   a. Anticonvulsants
   b. NSAIDs
   c. Opioids
   d. Stimulants

11). The principle of adjusting the dose of a medication until the desired effect is obtained is known as:
   a. Overprescribing
   b. Dosage Titration
   c. Ceiling Effect
   d. Multimodal Therapy

12). Meperidine (Demerol®) should not be used for chronic pain management because:
   a. It has a high abuse potential
   b. It's only available as an injectable
   c. It's too expensive
   d. Its metabolites may cause mental status changes and seizures

13). Disadvantages associated with the use of methadone include:
   a. Delayed-onset sedation may occur up to 2 weeks after onset of therapy.
   b. Due to a long half-life, repeated administration may lead to accumulation of the drug with a potential for significant toxicity
   c. It causes a prolonged but less severe withdrawal syndrome than morphine
   d. All of the above.

14). Which of the following is a mixed agonist-antagonist?
a. Nalbuphine
b. Levorphanol
c. Propoxyphene
d. Tramadol

15). Which of the following is NOT a disadvantage of Duragesic®?
a. Higher doses come in very large patches
b. Higher incidence of nausea and vomiting
c. Can take 24 hours to become effective
d. Relatively high cost

16). Which of the following products have both an immediate-release and a time-release component?
a. KADIAN® and Lortab™
b. Duragesic® and OxyContin®
c. OxyContin® and Avinza®
d. Oramorph® and MS Contin®

17). Which of the following drugs is NOT available in controlled-release form?
a. Morphine
b. Hydromorphone
c. Oxycodone
d. Fentanyl

Answers to Self-Assessment Test

1). d	7). d	13). d
2). a	8). b	14). a
3). a	9). c	15). b
4). a	10). a	16). c
5). d	11). b	17). b
6). c	12). d	

CHAPTER FOUR

Cancer Pain and Palliative Care

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the 6 general principles of treating cancer pain.
- Describe the role of anticancer therapies in treating cancer pain.
- Describe the 4 steps of the WHO pain treatment ladder.
- Describe the drugs commonly used in each step of the ladder.
- Discuss the use of potent opioids as step 3 of the WHO ladder.
- Discuss the phenomena of opioid tolerance and dependence.
- Discuss the use of adjuvant drugs to augment opioids.
- Discuss the use of nonpharmacologic interventions for cancer pain management.

Terminology

Adjuvant medications:	Medications used to help analgesics work better or that treat other symptoms associated with pain.
Catheter:	Any small tube used to carry fluids.
Ceiling effect:	For certain medications, when an increase in dose past a certain level does not result in any further effect.
Gamma knife:	Specialized machine that projects a very tightly focused beam of radiation.
Linear accelerator:	A machine that projects a beam of radiation.
Metastases:	Tumor that has spread to a new location.
Neurotoxic:	Damaging to nerve tissue.
Oncologist:	A physician specializing in cancer treatment.
Palliative:	Attempting to relieve symptoms without curing the disease.
Pathological fractures:	Fractures caused by tumor invading and destroying bone.
Radiotherapy:	General term for all types of radiation used to treat cancer.
Syndrome:	A group of findings or symptoms that commonly occur together.

Introduction

Pain is one of the most common symptoms experienced by cancer patients. Unfortunately, despite improvements during the last decade, cancer pain is often poorly managed. As a result, many patients experience needless suffering. Cancer pain, however, can be simpler to manage than chronic benign pain. In most patients, it can be effectively decreased with a simple medication regimen. This chapter describes some common strategies of effective cancer pain management, and particularly how opioid medications contribute to this plan.

General Principles of Pain Management

Almost all cancer patients will suffer significant pain at some point during the course of their disease. Many of these patients will respond very well to the routine medical management prescribed by their oncologist. A minority, however, will suffer persistent pain not relieved by such routine measures. These patients require a comprehensive clinical assessment, as described in Chapter 2, and therapy that is more intensive.

Whether the patient is managed with a simple prescription or with several different therapies, 6 general principles will always apply:

1) The patient must have an informed role in the management of the disease. The patient's condition and treatment options should be explained in understandable terms. Keeping the patient involved reduces anxiety and feelings of hopelessness and helplessness, increases compliance, and ensures that the patient's views remain paramount.

2) Involvement of the patient's family is important. The effects of cancer and cancer pain are almost as disruptive to the family as to the patient. The family will therefore require advice and support. At the same time, the family is a part of the patient's therapy and should be included in planning treatment.

3) A team approach is optimal. A collaborative effort between the patient, family, physicians, nurses, social workers, physiotherapists, dietitians, clergy, etc., provides the best possible care. When pain is not relieved by routine means, inclusion of a pain specialist in the team is helpful.

4) Treating the cancer is the first priority. Curative or palliative surgery, radiation therapy, hormonal therapy, and chemotherapy can remove or diminish the source of cancer pain, rather than just treat the symptoms.

5) All symptoms that cause distress, such as nausea, diarrhea, cough, constipation, insomnia, bedsores, incontinence, etc., should be treated.

6) The patient's environment is important. A comfortable and supportive setting reduces distress. Home is the best environment for most patients, as long as adequate support is available.

Anticancer Therapies

The initial focus of cancer treatment is to cure the patient of disease. Even when the cancer is not curable, appropriate chemotherapy, radiotherapy, or surgery may all be used to extend the patient's life and to reduce pain and other symptoms caused by the tumor. When the patient's pain is believed to result directly from the tumor invading the tissues of the body, anticancer therapy is the first priority.

When the pain is the result of tumor invading the tissues, anticancer therapy is the first priority.

These therapies all take time to work, however, and the patient's symptoms must be treated until the primary therapy becomes effective. Radiation or chemotherapy, for example, may take several months to shrink a tumor significantly. In terminal cases, the patient may have already received maximal doses of anticancer treatments. Control of symptoms is then the primary goal of therapy.

Radiation treatments relieve pain in several ways. Large tumors can cause pain by stretching or compressing surrounding tissues. Shrinking a large tumor with radiation can relieve much of this pain. Additionally, when tumors invade normal tissue they cause irritation, swelling, and destruction of the normal cells. Radiation not only slows cancer growth in such areas, it also reduces the inflammation and tissue irritation relieving much of the pain.

Radiation is usually delivered as a beam from an external radiation source, such as a linear accelerator or a "gamma knife". It can also be delivered to cancer cells by temporarily inserting radioactive material into a body cavity or an organ. This can be done by surgically implanting "seeds" of radioactive material, such as Cesium-137 or Iridium-192 directly into the area of tumor growth. Certain radioactive substances can also be injected into the bloodstream or taken by mouth. In these cases, the substance used is one that is selectively taken up by tissue that is the target of treatment. Orally ingested Iodine-131, for example, is selectively taken up by the thyroid gland and metastatic deposits of thyroid cancer. Strontium-89, another radioactive chemical, is taken up primarily by bone tissue, so it can selectively destroy metastatic cancer invading the bones.

Radiotherapy is most commonly indicated for localized pain from cancer invading a bone. It can also be effective when a tumor has nearly blocked a hollow structure in the body, such as the bowel or a bronchial tube. It is less effective for tumors invading nerves or soft tissues.